



## Phytochemical Profile and Anticancer Activity from Medicinal Plants Against Melanoma Skin Cancer: A Review

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### ABSTRACT

Melanoma skin cancer is a malignant melanocyte tumor considered the most invasive and dangerous skin cancer, with an average five-year survival rate of less than 5% after metastasis. Thus, a new strategy for preventing and treating cancer from the natural product is required. Medicinal plants are the potential as an alternative against cancer. This review article aims to determine natural products from medicinal plants which have the potential as an anticancer in melanoma skin cancer in vitro and in vivo. 40 plants have been selected based on the selection criteria for anticancer compounds. In vitro studies showed that the plant can reduce cell viability through cell cycle inhibition and apoptosis induction and inhibit angiogenesis, invasion, and metastasis in human melanoma skin cancer. Therefore, further research is required to explore more plants, especially medicinal plants, their active compounds, and the mechanism of anticancer action to be used as standard herbal medicines.

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## 1. INTRODUCTION

Skin cancer is one of the most common global public health problems, with increased mortality rates and morbidity and treatment costs annually (Thuncharoen et al., 2013; Yahya et al., 2019; Hwang et al., 2020). Despite the abundance of data on the presentation of skin cancer in white individuals, there is a paucity of data regarding disease morphology and risk factors in darker-skinned individuals because the incidence of skin cancer is relatively higher in white individuals (Gordon et al., 2022; Mancini et al., 2022). The leading cause of skin cancer is UV radiation. The intensity of UV exposure of more than 2.5 hours from the sun is absorbed by the skin, causing DNA damage, and inducing reactive oxygen species (ROS) in cells (Thuncharoen et al., 2013). Skin cancer is characterized by an imbalance of apoptosis or cell proliferation and survival in the epidermis. Skin cancer can be effectively eliminated by inhibiting the blood supply to the tumor (anti-angiogenesis), which inhibits tumor growth and improves patient survival (Yahya et al., 2019). According to their cellular origin, skin cancer is divided into melanoma skin cancer derived from melanocytes or Malignant Melanoma (MM) and non-melanoma skin cancer (NMSC) originating from epithelial cells (Hwang et al., 2020). Melanoma skin cancer is the most malignant skin cancer (in terms of invasive metastases), with a five-year survival rate averaging <5% (Liu et al., 2018; Hwang et al., 2020). An estimated  $\pm 100,350$  new cases of melanoma and 6,850 deaths were reported in the US in 2020 (Hwang et al., 2020; Ahmed et al., 2021). MM originates from pigment-bearing cells in the basal layer of the epidermis known as melanocytes (Zhou et al., 2016; Saginala et al., 2021). Melanocytes originate from the neural crest and express many molecules and signaling factors that promote migration and metastasis (Saginala et al., 2021). MM develops from the proliferation of

melanocyte cells that arise where melanocyte cells are located. In addition, MM has a poor prognosis because of its potential to metastasize (Yahya et al., 2019). MM is divided into several clinical subtypes that differ in presentation, demographics, and molecular profile. Superficial spreading melanoma is the most common type, especially in fair-skinned individuals. Acral lentiginous melanoma arises from the glabrous skin on the palms, soles, and nail bed, occurs in dark-skinned people, and uveal melanoma has an inferior prognosis. More than 50% of patients have stage IV disease (Saginala et al., 2021).

Standard cancer treatment includes surgery, chemotherapy, radiation therapy, and immunotherapy. However, to date, there is no effective strategy to treat melanoma in clinical practice due to the side effects of chemotherapy and the development of multidrug resistance (Kim et al., 2018; Yang et al., 2018; Khalifa et al., 2019; Tuzimski et al., 2021). Therefore, it is necessary to find an efficient, effective drug with fewer side effects and toxicity to treat melanoma (Kim et al., 2018; Yang et al., 2018; Abdulridha et al., 2020). Several studies have revealed that the phytochemical content of natural products has an anticancer activity that is very safe, non-toxic, readily available, and cost-effective (Khan et al., 2019; Mistiogiani et al., 2021; Tuzimski et al., 2021).

Natural products and their synthetic analogs represent a source of new drugs; about 80% of approved chemotherapy drugs and more than half of all drugs are based on bioactive natural products. Many natural-derived metabolites act as antitumor agents through solid growth inhibition in vitro human tumor cell models (Khalifa et al., 2019). From the history of drug discovery, natural product-derived compounds can be a promising treatment because of their characteristics to induce apoptosis more frequently in cancer than in normal cells. Several chemotherapeutic agents, including Taxol, epothilones, and vinca alkaloids, are

derived from natural products (Kim et al., 2018). The development of cancer drugs from natural products is currently a trend to minimize chemotherapy side effects and resistance. Studies related to specific articles on melanoma skin cancer are still limited. Thus, this review can be a reference for future studies in developing research on melanoma skin cancer originating from natural products. Therefore, this article review aims to determine the anticancer activity of natural products on human melanoma skin cancer cells.

## 2. METHOD

A comprehensive literature review relevant to the study topic was performed in PubMed, Scopus, and Google Scholar from February 2022 to May 2022 using advanced search builders (see **Figure 1**). The keywords and phrases used during the search were “Medicinal Plants”, “Natural products”, “Anticancer activity”, and “Human melanoma skin cancer”. Articles were included based on the following criteria:

- (i) The studies primarily focus on the activity of the natural product in skin cancer melanoma
- (ii) The studies using an in vitro and in vivo approach
- (iii) The study's full texts were available
- (iv) The studies were research article
- (v) Melanoma is a malignant tumor of melanocytes and is considered the most invasive and dangerous skin cancer.

The number of relevant articles finalized after extraction and analysis through the combination of the above keywords/phrases and the inclusion criteria was 275. The inclusion was based on two sets of criteria. According to the first set, i.e., “general criteria,” articles selected for this manuscript had (i) reported the traditional anticancer activity of medicinal plants and their parts, (ii) reported the anticancer role of extract or pure compounds from medicinal plants.

The second set of criteria was used for selecting specific anticancer plants whose

phytochemicals are discussed in detail. For this purpose, thirty-nine plants were selected for which recent articles were available that (a) studied in vitro anticancer activities of herbal products and (b) reported the anticancer/antitumor activity of active compounds from the plants.

All the data were extracted in a table and the mechanisms of action were explained in respective subheadings and demonstrated through different figures.

Several abbreviations were used: 1,2-dihydroxyxanthone (1,2-DHX); Astrocyte-elevated gene-1 (AEG-1); Apoptotic peptidase activating factor 1 (Apaf-1); Apoptosis signal-regulating kinase 1 (ASK1); Bcl-2 associated X protein (Bax); B-cell lymphoma protein 2 (Bcl-2); B-cell lymphoma-extra-large (Bcl-xl); Bcl-2-interacting mediator of cell death (BIM); Cysteine-aspartic proteases (Caspase); Cell division cycle gene 25 (CDC25); Cyclin dependent kinase 1 (CDK1); Cyclin dependent kinase (CDKs); Checkpoint kinase ½ (CHK1/2); Cytochrome c (Cyt-c); Deoxyribonucleic Acid (DNA); Half maximal effective concentration (EC50); Epithelial-mesenchymal transition (EMT); Focal adhesion kinase (FAK); Growth 1/0 (G1/G0); Growth 2/ mitosis (G2/M); Synthesis (S); Ferrous (Fe<sup>2+</sup>); Growth factor receptor-bound protein 2 (GRB2); Human keratinocyte cell line (HaCaT cell); Hypoxia-inducible factor-1α (HIF-1α); Half maximal inhibitory concentration (IC50); c-JUN N-terminal kinase (JNK); Inhibitor of NF-κB (IκB); Inhibitor of NF-κB alpha (IκBα); Mitogen-activated protein kinase (MAPK); Michigan cancer foundation-7 (MCF-7); Myeloid cell leukemia-1 (Mcl-1); Malignant Melanoma (MM); Matrix Metalloproteinase (MMP); Matrix Metalloproteinase-1, 13, 2, 9 (MMP-1, 13, 2, 9); Messenger Ribonucleic Acid (m-RNA); Nuclear factor kappa B (NF-κB); Non-melanoma skin cancer (NMSC); Akt strain transforming protein (p-Akt); Poly [ADP-Ribose] Polymerase (PARP); Phospho-c-jun (p-c-jun); Phosphorylated-Epidermal growth

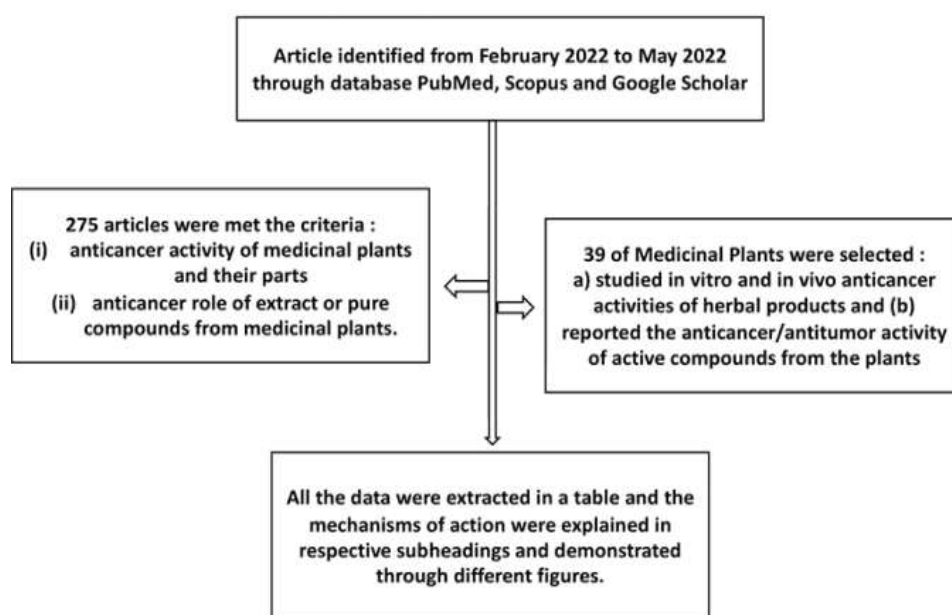
factor receptor (p-EGFR); Extracellular signal-related kinase ½ (p-ERK ½); Phosphoinositide 3-kinase (PI3K); Phosphorylated-mammalian target of rapamycin (p-mTOR); Retinoblastoma protein (pRb); P53 upregulated modulator of apoptosis (PUMA); Reactive Oxygen Species (ROS); Specific deSUMOylation protease 1 (SENP1); Second mitochondrial activator of caspases/direct IAP binding protein with low PI (Smac/DIABLO); Small Ubiquitin-like Modifier (SUMO); Human ductal breast cancer epithelial tumor cell line (T47D); Tissue inhibitor of metalloproteinase (TIMP-1); Ultraviolet (UV); Vascular endothelial growth factor (VEGF); X-linked inhibitor of apoptosis protein (x-IAP).

### 3. RESULTS

Melanoma is a life-threatening malignancy with a high rate of metastasis and mortality. Approximately 232,000 melanoma patients were newly diagnosed in 2011, with 55,000 deaths recorded in the same year (Huang et al., 2020). The incidence of malignant melanoma has increased over the last 25 years in the UK, but the death rate has remained relatively constant. The 5-year survival rate ranges from 20% to 95%,

depending on the stage of the disease. The incidence of melanoma varies widely in different populations and is about 10 to 20 times higher in the white population than in the non-white population. The age-adjusted incidence of melanoma per 100,000 population is 21 in the US, 17 in the UK, and 50 in Australia. Australia has the highest prevalence of melanoma in the world (Pay, 2016).

Malignant melanoma is a tumor originating from melanocytes in the basal layer of the epidermis. Cancer cells become invasive and penetrate and outside the dermis and into the epidermis after malignant transformation. Malignant melanoma is described by the histopathological grade of dermal invasion (Clark level I–V) and by clinical staging ranging from stage 1 to 4 based on tumor thickness, presence of ulceration, and presence of nodal and distant metastatic disease (Slominski et al., 2001; Pay, 2016). Melanoma susceptibility is influenced by genetic factors, such as familial incidence of melanoma, racial background, skin type, and gender; constitutional factors, such as age, number, size, and type of pigmented nevus; and environmental factors, such as accumulated lifetime sun exposure.



**Figure 1.** Literature review flow chart.

Melanomas that produce growth factors, cytokines, and corresponding receptors can potentially self-regulate their tumor behavior. For example, the expression of receptors for proopiomelanocortin-derived neuropeptides (POMC), melanocyte-stimulating hormone (MSH), and adrenocorticotrophic hormone (ACTH) are known to modify normal and malignant melanocyte phenotypes.

Melanoma also produces other growth factors and cytokines, such as keratinocyte growth factor, platelet-derived growth factor-A, platelet-derived growth factor-B, stem cell factor, melanoma growth-stimulating activity, interleukin (IL)-1 $\alpha$ , IL-1 $\beta$ , IL-6, IL-7, IL-8, IL-10, IL-12, granulocyte-macrophage colony-stimulating factor, granulocyte colony-stimulating factor, TNF- $\alpha$ , interferon- $\gamma$ , and interferon- $\beta$  (Slominski et al., 2001).

Human skin malignant melanoma remains the deadliest form of skin cancer. Many human melanoma cell lines used in this study were derived from biopsies of primary malignant or metastatic melanoma, as shown in **Table 1**.

### 3.1. *Ailanthus Altissima*

*Ailanthus altissima* (Mill.) Swingle, known as the tree of heaven, is widespread in Europe and North America (Sladonja et al., 2015), China (Okunade et al., 2003), and Korea (Meihua et al., 2009), belonging to the Simaroubaceae family (Sladonja et al., 2015). *A. altissima* is mainly found in cities, agricultural fields, and transportation corridors (Caramelo et al., 2021). *A. altissima* is used in traditional Chinese medicine uses it to treat certain disorders such as epilepsy, diarrhea, asthma, eye diseases, and seborrhoea. In addition, the bark is used for dysentery, menorrhagia, and spermatorrhea. For intestinal problems lasting several months, it is recommended to boil the bark with water and then drink the liquid along

with gin (Kowarik et al., 2007; Sladonja et al., 2015; Caramelo et al., 2021).

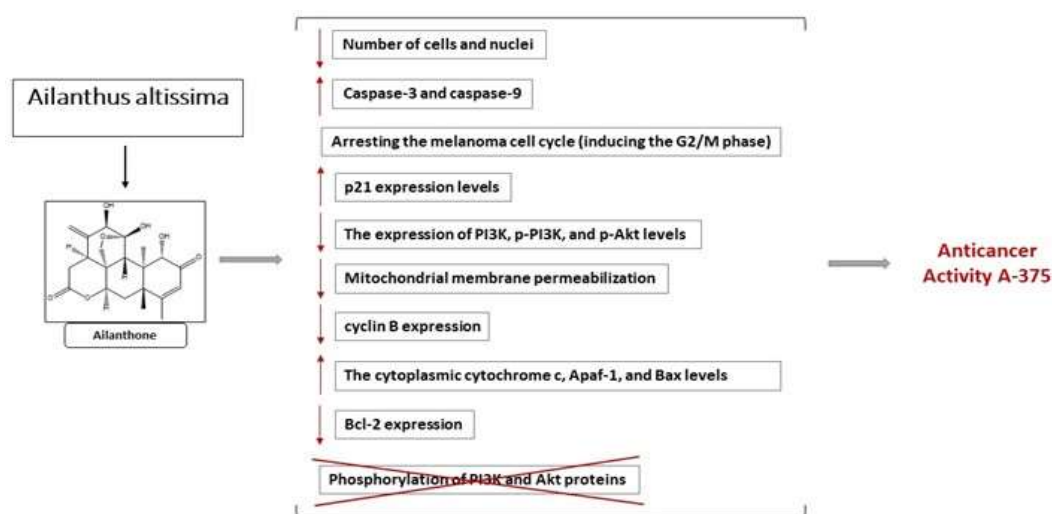
It is rich in alkaloids, terpenoids, sterols, flavonoids, and other compounds. The compounds in the *Ailanthus* plant have been studied extensively and have been the subject of several studies due to their pharmacological activities (Kundu et al., 2010; Caramelo et al., 2021). The bark contains oleoresin, resin, ceryl alcohol, ailanthin, isoquercetin, tannin, ceryl palmitate, and saponins (Kowarik et al., 2007). The root bark contains alkaloids, terpenoids, ligands, coumarins, phenylpropanoids, and terpenoids (Kundu et al., 2010; Yang et al., 2014; Zhang et al., 2020a; Du et al., 2021). The leaves of this plant contain tannins, quercetin, isoquercetin, alkaloids, and flavonoids (Kundu et al., 2010) which are widely used in traditional Indian medicine to treat seborrhoea and scabies (Kowarik et al., 2007).

Ailanthone (**Figure 2**) isolated from *A. altissima* has abundant pharmacological activities, including anti-tuberculosis, antiviral, and antitumor (Sladonja et al., 2015; Liu et al., 2020). It significantly inhibits cancer cell proliferation, migration, invasion, and metastasis. Ailanthone significantly decreases the viability of A375 cells with an IC<sub>50</sub> value of 5.77  $\mu$ M by arresting the melanoma cell cycle, thus inducing the G2/M phase. It also increases p21 expression levels and decreases cyclin B expression in A375 cells.

Ailanthone also significantly decreases the expression of PI3K, p-PI3K, and p-Akt levels in A375 cells and decreases mitochondrial membrane permeabilization, increasing the cytoplasmic cytochrome c, Apaf-1, and Bax levels and decreasing Bcl-2 expression in ailanthone-treated A375 cells, significantly (Liu et al., 2020). The activity of ailanthone on other melanoma cell lines is yet not found in other cells

**Table 1.** Human melanoma cell line.

No.	Name	Biopsy Site	References
1.	A2058	Lymph node	(Su et al., 2009)
2.	A375	Skin	(Su et al., 2009)
3.	C32	Skin	(Su et al., 2009)
4.	COLO829	Skin	(Su et al., 2009)
5.	G361	Skin	(Su et al., 2009)
6.	HT144	Skin	(Su et al., 2009)
7.	HTB65	Lymph node	(Su et al., 2009)
8.	RPMI7951	Lymph node	(Su et al., 2009)
9.	SKMEL24	Skin of thigh	(Su et al., 2009)
10.	SRS3	Back	(Su et al., 2009)
11.	UACC3074	Unknown	(Su et al., 2009)
12.	WM266-4	Skin	(Su et al., 2009)
13.	C8161	Unknown	(Su et al., 2009)
14.	MUM2C	Liver	(Su et al., 2009)
15.	UACC1227	Lymph node	(Su et al., 2009)
16.	UACC2265	Lymph node	(Su et al., 2009)
17.	UACC457	Abdomen	(Su et al., 2009)
18.	UACC827	Right breast	(Su et al., 2009)
19.	UACC903	Back	(Su et al., 2009)
20.	UACC903(+6)	Back	(Su et al., 2009)
21.	UACC929	Lymph node	(Su et al., 2009)

**Figure 2.** The mechanism of Ailanthone.

### 3.2. Berberis aristata

*Berberis aristata* found in sub-Himalayan areas. It considered the most essential herbal plant in the Ayurvedic, Siddha, and Unani systems of medicine because of its medicinal importance (Ramawat et al., 2008). Traditionally, it is used as a tonic, sedative, diaphoretic, diuretic, and alternative to treat diseases such as wound healing, skin diseases,

rheumatism, snake bites, menorrhagia, jaundice, and eye problems (Shinwari et al., 2010; Chander et al., 2017). In India and Nepal, this plant used to treat allergies, metabolic disorders (Joshi & Joshi, 2007), cholera, acute diarrhea (Dutta et al., 1962; Lahiri et al., 1967), latent malaria, amoebiasis, ophthalmia, eye diseases and acts as a laxative (Joshi et al., 2007). Almost all parts of *Berberis aristata* contain various chemical constituents, which berberine as

the main constituent (Murad et al., 2007; Choudhary et al., 2021). It is present in leaves, roots, rhizomes, and bark (Murad et al., 2007). In addition, the flowers of the *B. aristata* plant contain a polyphenolic flavonoid named quercetin, meratin, and rutin (Sivakumar et al., 1991).

Berberine (Figure 3) is an isoquinoline alkaloid isolated from the roots and bark of the *B. aristata*. It has broad pharmacological activity, including antimicrobial, anti-inflammatory, antioxidant, and anticancer activities. Berberine decreases cancer cell viability by induction of cell cycle arrest and apoptotic cell death (Liu et al., 2018). It induces changes in cell morphology and reduces the number of A375.S2 cells. In addition, berberine significantly suppresses motility and migration. It also inhibits the invasion of A375.S2 cells in vitro, which inhibits metastasis-associated proteins such as FAK, RhoA, ROCK1, or p-AKT, NF- $\kappa$ B, and uPA, leading to MMP-1 inhibition and MMP-13.

Berberine also increases E-cadherin and decreases N-cadherin in A375.S2 cells, whereas decreased E-cadherin and increased N-cadherin levels played essential roles in cancer cell migration and invasion.

Furthermore, this study found that berberine suppressed the mobility of PLX4032-resistant A375.S2 cells (A375.S2/PLX cells) (Singh et al., 2011; Liu et al., 2018). The activity of berberine compounds has not found against other skin cancer melanoma cell lines.

### 3.3. Piper Betle

*Piper betle* Linn belongs to Piperaceae family and is mainly found in Southeast Asia, Malaysia, Guangdong, Java, Indonesia, the Philippine Islands, East Africa, and Taiwan. Piper species have been used in a variety of traditional medicine, including traditional Chinese medicine, Latin American folklore medicine, and Ayurvedic therapy in the West Indies (Khan et al., 2011; Yang et al., 2018a; Wu et al., 2020). In some areas, such as Taiwan and India, *P. betle* has been shown to have antioxidant, antimicrobial, and anti-hemolytic activity (Kumar et al., 2010; Chakraborty et al., 2011; Rai et al., 2011). The high content of various bioactive constituents, including lignin, polyphenols, alkaloids, steroids, saponins, tannins, flavonoids, and terpenes found in the leaves and stems of *P. betle* (Nagori et al., 2011).

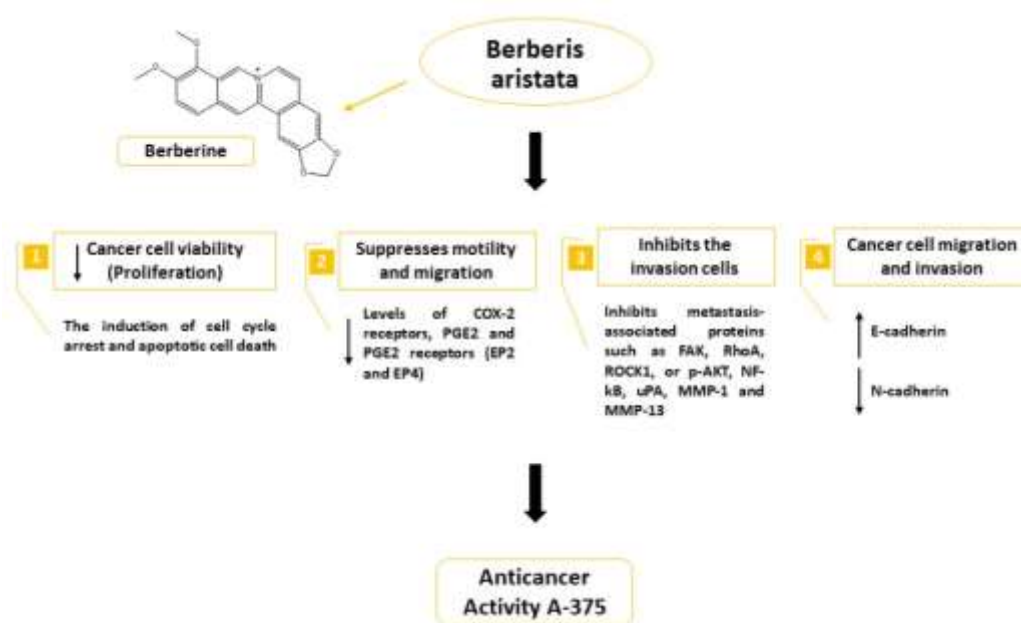
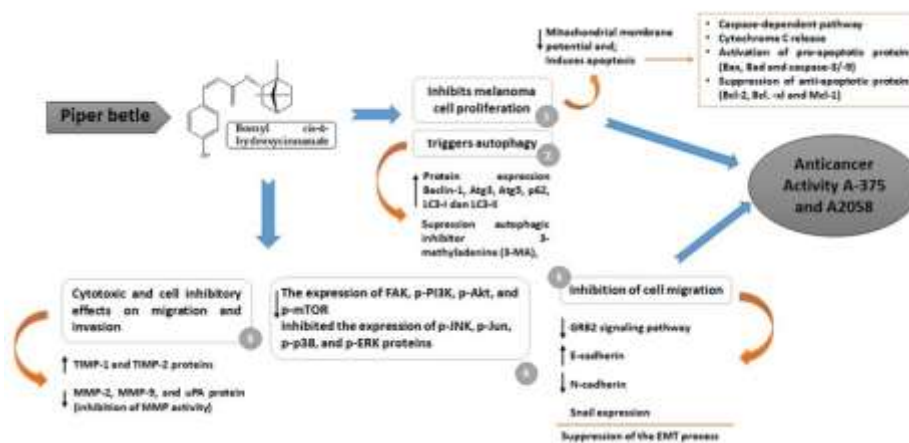


Figure 3. The mechanism of berberine.

*P. betle* contains several compounds, including allylpyrocatechol diacetate, allylpyrocatechol monoacetate, campene, caryophyllene, chavibetol, chavibetol acetate, chavibetol methyl ether, 1-8-cineol, eugenol, u-limonene,  $\alpha$ -pinene, f-pinene, and saprobe which known for their activity as antibacterial, antileishmanicidal, antifilaria, antifungal, antimalarial, larvicidal, and antiproliferative activities. In addition, *P. betle* extract has also been found to have hepatoprotective and anticancer properties. Bornyl cis-4-hydroxycinnamate contained in *P. betle* is known for its activity as an anticancer in the MAPK signaling pathway (Figure 4) (Yang et al., 2018a). Bornyl cis-4-hydroxycinnamate (12  $\mu$ M concentration) provides cytotoxic and cell inhibitory effects on migration and invasion in A375 cells (Yang et al., 2018a). In addition, it upregulates TIMP-1 and TIMP-2 proteins and down-regulates of uPA protein, which plays an essential role in inhibiting MMP activity and anti-invasion properties in melanoma cancer cells. It also decreases the expression of FAK, p-PI3K, p-Akt, and p-mTOR in A375 cells and inhibits the expression of p-JNK, p-Jun, p-p38, and p-ERK proteins (Yang et al., 2018a). Bornyl cis-4-hydroxycinnamate also involves the GRB2 signalling pathway, which decreased after being treated with Bornyl cis-4-hydroxycinnamate. It is associated with cell migration. On the other hand, it increases E-cadherin expression. It decreases N-cadherin expression and Snail expression,

which is associated with the inhibition of cell migration through suppression of the EMT process. EMT is a phenotypic transformation due to impaired cell-cell interaction and adhesion and facilitates cell motility (Yang et al., 2018a). The results showed that bornylcis-4-hydroxycinnamate inhibited the viability of A2058 melanoma cells. In addition, Bornyl cis-4-hydroxycinnamate inhibited the migration and invasion of A2058 melanoma cells, whereby the migratory ability of A2058 cells was reduced to about 70%. The protein levels of MMP-2, MMP-9, and uPA were decreased, and TIMP-1 and TIMP-2 were increased in A2058 cells after treatment with bornyl cis-4-hydroxycinnamate for 24 h. There was a decrease in the expression of phosphorylated proteins FAK/PI3K/Akt/mTOR signaling-associated proteins (Akt, p-Akt, PI3K, p-PI3K, mTOR, p-mTOR, FAK) and MAPKs signaling pathway-related proteins (JNK, p-JNK, Jun, p-Jun, p38, p-p38, ERK, and p-ERK) in A2058 cells after treatment with bornyl cis-4-hydroxycinnamate. Signal levels of GRB2 pathway proteins (GRB2, Rac, PKC, Ras, RhoA, MEKK3, and MEKK7) were decreased in A2058 cells. In addition, N-cadherin protein levels decreased, and E-cadherin increased in A2058 cells after treatment with bornyl cis-4-hydroxycinnamate, and Snail protein levels in the nucleus were also decreased (Yang et al., 2018a).



**Figure 4.** The mechanism of Bornyl cis-4-hydroxycinnamate.



This study conducted a (+)-bornyl p-coumarate examination on A2058 melanoma cells. The inhibitory effect of (+)-bornyl p-coumarate on cell lines was assessed by 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay and the underlying mechanism identified by immunostaining, flow cytometry and western blotting of proteins associated with apoptosis and autophagy. The results showed that (+)-bornyl p-coumarate inhibited melanoma cell proliferation and caused a loss of mitochondrial membrane potential, suggesting that the treatment induces apoptosis. Moreover, western blotting revealed that the process is mediated by a caspase-dependent pathway, cytochrome C release, activating proapoptotic proteins (Bax, Bad, and caspase-3/-9), and suppression of antiapoptotic proteins (Bcl-2, Bcl.-xl and Mcl-1). Also, the regulated expression of p-PERK, p-eIF2 $\alpha$ , ATF4, and CCAAT/enhancer-binding protein (C/EBP)-homologous protein (CHOP) after treatment indicated that (+)-bornyl p-coumarate induces reticulum endoplasmic (ER) stress-mediated apoptosis.

In addition, increased expression of the proteins beclin-1, Atg3, Atg5, p62, LC3-I, and LC3-II and suppression by the autophagic inhibitor 3-methyladenine (3-MA), suggest that (+)-bornyl p-coumarate triggers autophagy in melanoma cells (Wu et al., 2020). The in vivo data regarding this chemical against melanoma skin cancer is searched, yet not found.

### 3.4. *Ananas Comosus* (L.) Merr.

*Ananas comosus* or pineapple belongs to the Bromeliaceae family. Pineapple has been used as a medicinal plant in several countries worldwide. Pineapple leaves, stems, and fruit contain many vitamins, organic acids, sugars, and proteinase enzymes, including bromelain and peroxidase (Pavan et al. 2012; Monji et al. 2015). In addition, it contains many secondary metabolites, including phenolics, flavonoids, and isoflavone, which

provide pharmacological activity, including antirheumatic, anticancer, antimicrobial, wound healing, cardiac protective, hepatoprotective, antidiabetic, uterotonic, antioxidant, and anthelmintic. It also has a bromelain enzyme, which possesses anticancer activity (Figure 5) (Debnath et al., 2021).

Bromelain inhibits the proliferation and reduces the growth of A375 cell lines by suppressing the abnormal growth of cancer cells. It also induces apoptosis in A375 cells by reducing intracellular GSH content and increasing ROS production, thus leading to mitochondrial membrane depolarization and apoptosis. In addition, bromelain also affects NF-kB translocation and suppresses I $\kappa$ B $\alpha$  phosphorylation.

The release of NF-kB from I $\kappa$ B $\alpha$  results in NF-kB translocation and binding to specific sequences in the promoter region of the target gene. The basal level of the p65 subunit of NF-kB was increased in the nucleus of A375 cells, leading to the inhibition of transcription factor translocation (Bhui et al., 2012). The activity of bromelain in other melanoma skin cancer cell lines was not found.

### 3.5. *Passiflora caerulea* (blue passion flower)

*Passiflora caerulea* L. (Passifloraceae) is widely distributed in South America, traditionally considered a medicinal, ornamental, and edible plant. Its activity is associated with its traditional role as an anxiolytic and sedative, which has been validated to some extent through the identification of flavonoids as responsible for this activity (Deginiani 2001; Mondin et al. 2011; Aquino & Garcia 2019; Minteguiga et al., 2021).

In addition, it is used in digestive disorders, anti-inflammatory, anthelmintic, diuretic, emmenagogue, antiscorbutic, and anti-icteric uses (Alonso & Desmarchelier., 2005). The root infusion is also used for the treatment of pneumonia and as an

anthelmintic (Bandoni et al., 1972; El-Askary et al., 2017). *P. caerulea* is rich in flavonoids, including chrysin and C-glycosides, including vitexin, isovitexin, orientin, isoorientin, and vicenin-2) (Figure. 6) (Minteguiaga et al., 2021). Chrysin (5,7-dihydroxyflavone) is a polyphenolic compound with various biochemical and pharmacological activities in cancer prevention. Chrysin inhibits cell mobility, migration, and invasion of A375.S2 cells. In addition, chrysin inhibits MMP-2 activity, and GRB2, SOS-1, PKC, p-AKT

(Thr308), p-AKT(Ser473), NF-Bp65, NFkBp50 Ras, PI3K, p-cJun, dan Snail expression in A375.S2 cells. p-AKT(Ser473) at 24 hours of treatment. Furthermore, It also decreases the uPA, N-cadherin, MMP1, MMP-2, and VEGF expression and increases E-cadherin expression (Chen et al., 2019a).

The activity of chrysin in other melanoma skin cancer is also not found while finding the literature. On the other hand, the in vivo assay is also not found while finding the literature.

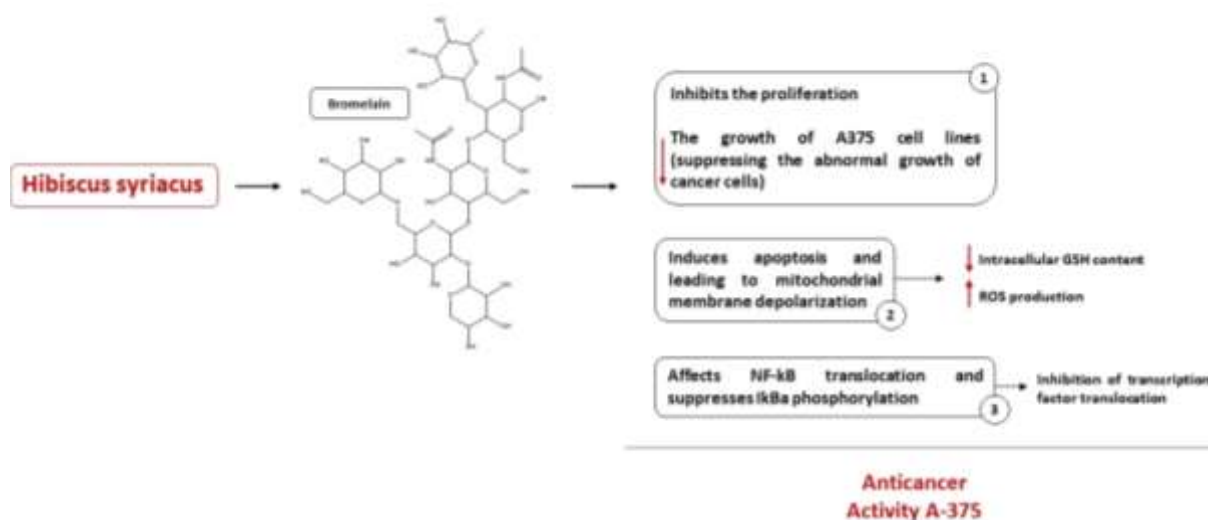


Figure 5. The mechanism of bromelain.

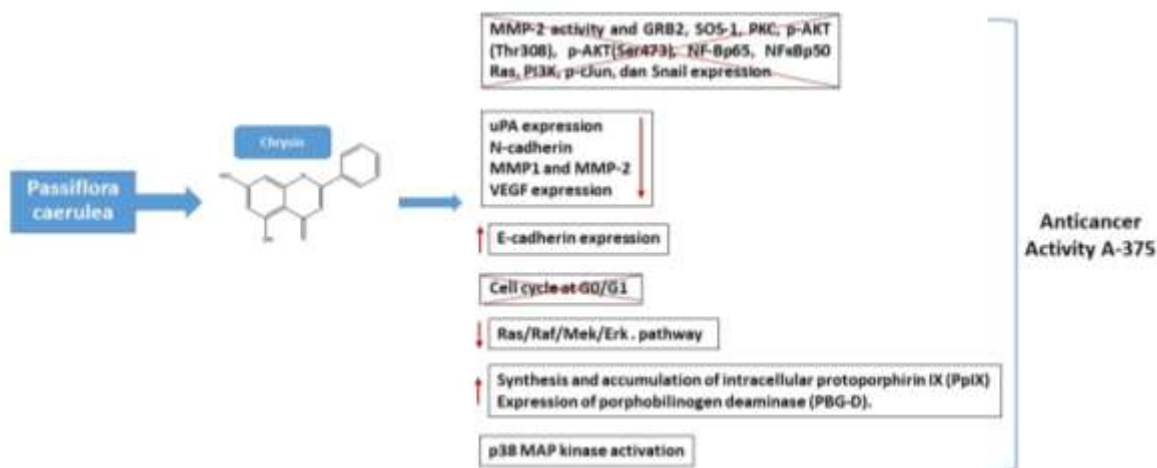


Figure 6. The mechanism of chrysin.

### 3.6. *Matricaria chamomilla* L.

Chamomile (*Matricaria chamomilla* L.), also known as German chamomile, is an aromatic plant that belongs to the Asteraceae family. It is one of the most prominent families, with more than 23,000 species belonging to more than 1900 genera (Jeffrey, 2007). The biological activity of various types of extracts is caused by the phytochemical content that belongs to the flavonoid group (apigenin, luteolin, quercetin, patuletin) and essential oils ( $\alpha$ -bisabolol and its oxide, azulenes) (Srivastava et al., 2009).

The main biological activities include antioxidant, antimicrobial, anti-inflammatory, cytotoxic, antispasmodic, antiviral, and sedative potential (Srivastava et al., 2009; Park et al., 2017). Chamomile flowers are also used to relieve colic spasms in young children. Cosmetically, it is used as a rinse for blonde hair and as topical preparations for eczema and skin disorders (Hoerman, 1994).

Chamomile extract was also reported to induce apoptosis in cancer cells but not in normal cells at the same dose (Srivastava et al., 2007). Apigenin from *Matricaria chamomilla* L. or Chamomile is known for its chemopreventive properties (Figure 7). Aside apigenin, it also contains luteolin, quercetin, patuletin,  $\alpha$ -bisabolol and azulena. Chamomile has broad pharmacological activity, including antioxidant, antimicrobial, anti-inflammatory, cytotoxic, antispasmodic, antiviral, and sedative potential.

The antiproliferative activity of chamomile extract is potential for various cell lines, including human prostate epithelial PZ-HPV-7 cells, LNCaP human prostate cancer, DU145, PC-3 cells, T-47D breast carcinoma, HeLa cervical adenocarcinoma, HT1080-fibrosarcoma, and RKO cell carcinoma -colon (Danciu et al., 2018). Chamomile extract provides weak antiproliferative and proapoptotic properties in A375 human

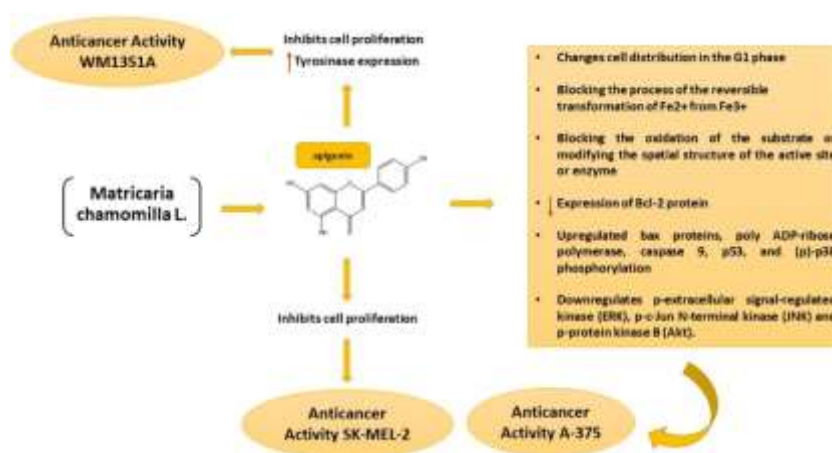
melanoma cells and significantly changes cell distribution in the G1 phase. It is related to the antioxidant properties of chamomile extract, which scavenges free radicals and iron chelation potency by blocking the process of the reversible transformation of Fe<sup>2+</sup> from Fe<sup>3+</sup> and blocking the oxidation of the substrate or modifying the spatial structure of the active site or enzyme (Danciu et al., 2018).

Sulforhodamine B assay measured the cytotoxic activity of methanol extract from chamomile flowers. Sulforhodamine B cytotoxic assay was performed in the concentration range of 0.8-100  $\mu$ g/ml to determine the dose at which 50% of cell growth was inhibited. Cytotoxic activity of chamomile flower extract on cells against SK-MEL-2 melanoma cells (IC<sub>50</sub> value 40.7  $\mu$ g/ml) (Sak et al., 2017).

A study was conducted on methanol extract from the *Matricaria chamomilla* L. (Chamomile) plant. The antiproliferative effect of the extract was tested on WM 1361A (high tyrosinase expression) using the MTT test. The results showed that M. chamomilla methanol extract inhibited the proliferation of melanotic WM1361A with an IC<sub>50</sub> value of 25.2 g/ml (Fraihat et al., 2018).

### 3.7. *Glycyrrhiza inflata*

Licorice (*Glycyrrhiza* spp.) is one of the oldest herbal medicines, which roots and rhizomes of *Glycyrrhiza inflata* have been widely used for various pharmaceutical applications for thousands of years. It can be found throughout Central Asia (Kyrgistan, Kazakhstan, Tajikistan, Turkmenistan, Uzbekistan, and Mongolia) and western China (Hayashi and Sudo., 2009; Jun et al., 2010). The roots and rhizomes of *Glycyrrhiza inflata* have been widely used as excipients for various pharmaceutical applications for thousands of years in southern Europe and Asia (Wang et al., 2013; Guo et al., 2013a).



**Figure 7.** The mechanism of apigenin.

One of the primary sources in Chinese medicine is licorice root because of the presence of various active ingredients, such as triterpenoids, flavonoids, and polysaccharides (Guo et al., 2013a; Shen et al., 2015) which exhibit several pharmacological activities such as anti-allergic, anti-inflammatory, antiviral, anxiolytic, and anticarcinogenic activity (Manthey et al., 2001; Teillet et al., 2008; Boumendjel et al., 2009; Guo et al., 2013a). The roots of *Glycyrrhiza inflata* are a source of phenolic compounds such as retrochalcone. Six retrochalcones (licochalcones A-E and echinatin) have been isolated and characterized from the roots of *G. inflata* (Yoon et al., 2005; Guo et al., 2013b; Si et al., 2018). *G. inflata* contains various active ingredients, such as triterpenoids, flavonoids, and polysaccharides (Zhao et al., 2018). Licochalcone D (LD) (Figure 8) is a flavonoid compound mainly found in the root of *Glycyrrhiza inflata*, which has antioxidant and anti-inflammatory properties (Si et al., 2018). Licochalcone D (LD) inhibits proliferation, induces apoptosis, and inhibits migration and invasion of A375 cells. LD induces apoptosis through the mitochondrial-mediated pathway by inducing mitochondrial membrane potential ( $\Delta\Psi_m$ ) loss, which increases intracellular ROS. The migration and invasion of A375 cells are also inhibited by downregulating MMP-9 and MMP-2 downregulation (Si et al., 2018).

Licochalcones A and E retrochalcones or reversely constructed chalcones, isolated from the roots of *Glycyrrhiza inflata*, were evaluated for cytotoxicity against the SK-MEL-2 (melanoma) cell line using the sulforhodamine B (SRB) assay. The effect of this compound on the inhibitory activity of DNA topoisomerase I (topo I) was also measured using the supercoiled DNA unwinding assay. All compounds showed moderate cytotoxicity against the SK-MEL-2 cell line and inhibited topo I activity (Yoon et al., 2007). Licochalcone B (Lico B) isolated from the roots of *G. inflata* (Chinese Licorice) significantly inhibited cell proliferation and induced apoptosis of A375 cells through regulation of specificity protein 1, CCAAT homologous protein/enhancer-binding protein, death receptors, and poly (ADP-ribose) polymerase (Kang et al., 2017). One of the anticancer activity compounds for melanoma is Licochalcone H (LCH). The results obtained that LCH 5, 10, 20, and 30  $\mu\text{M}$  inhibited cell growth and induced apoptosis, accompanied by cessation of the cell cycle in the G1 phase. Western blot analysis showed that JAK2 and STAT3 phosphorylation was decreased. Inhibition of the JAK2/STAT3 signaling pathway by inhibitors of JAK2/STAT3 (cryptotanshinone (CTS) and S3I-201) suggests that LCH induces apoptosis by modulating JAK2/STAT3 signaling (Park et al., 2022). In vivo study related to licorice is not intensively studied yet as anti-melanoma skin cancer.

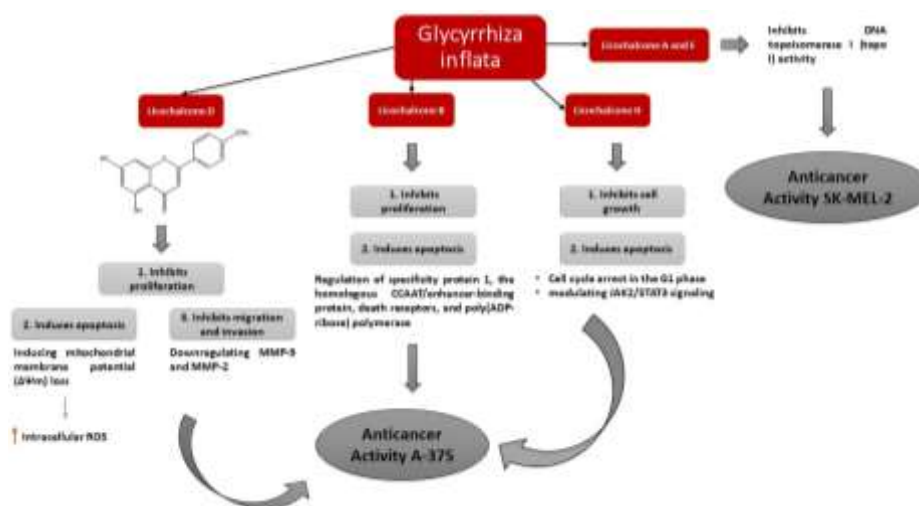


Figure 8. The mechanism of licochalcone D.

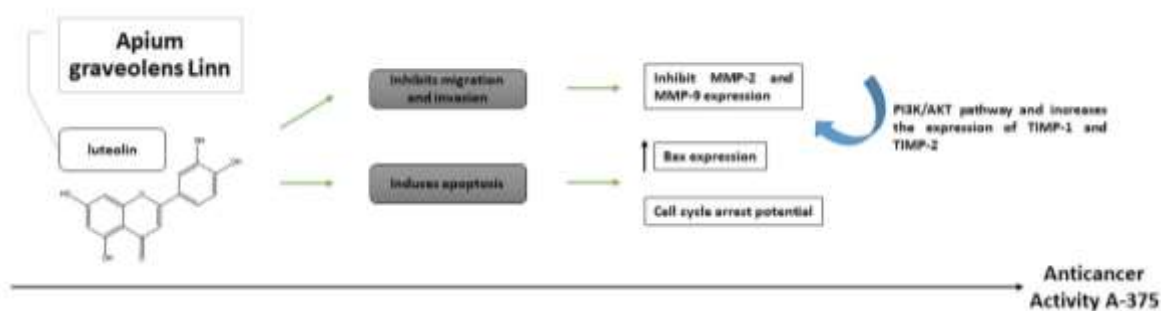
### 3.8. *Apium graveolens* Linn.

*Apium graveolens* Linn or Celery belongs to the Apiaceae. It grows annually under certain conditions, flowers from June to August, and the seeds ripen from August to September. Celery as an essential garden crop, widely cultivated in temperate climates (Jain et al., 2013), spreads in the northern hemisphere of Europe, spreading east to western Asia and south to north and east Africa (Ronse et al., 2010), and leaf stems are used as popular vegetables. In India, celery seeds are used to treat asthma, bronchitis, and spleen disease. Also, in the Indian system, *Apium graveolens* L seeds are used as medicine for treating liver diseases (Jain et al., 2013; Qureshi et al., 2014). The phytochemical content of celery has shown the presence of polyphenols, flavonoids, steroids, tannins, saponins, and terpenoids.

Luteolin (3',4',5,7-tetrahydroxyflavone) (Figure 9) is a flavonoid found in celery that has a hepatoprotective, cytotoxic, anti-inflammatory effect, anti-estrogenic, and antioxidant (Uddin et al., 2012; Yao et al., 2019; Minaiyan et al., 2021) Luteolin inhibits A375 cell proliferation and induces apoptosis by increasing Bax expression (Yao et al., 2019). It also inhibits the migration and invasion of A375 cells by inhibiting MMP-2 and MMP-9 expression through the PI3K/AKT pathway and increases the expression of

TIMP-1 and TIMP-2, which are negative regulators of MMP. On the other hand, an animal model of xenograft tumor was used to investigate the anticancer effect of luteolin on A375 cell growth in vivo, which showed that luteolin significantly inhibited the growth of A375 cells in a xenograft mouse model (Yao et al., 2019). Luteolin has considerable cytotoxicity against A375 cells with an IC50 value of 115.1  $\mu$ M. Luteolin also inhibits colony formation and induces apoptosis by disrupting cellular integrity. In addition, the accumulation of cells in the G0/G1 phase (60.4-72.6%) after 24 hours of treatment indicates the potential for cell cycle arrest of this compound (George et al., 2013).

Celery extract is rich in polyphenol and flavonoid compounds and produces radical scavenger capacity, iron chelation potential, and lipoxygenase inhibitory capacity. Celery extract had significant antiproliferative and proapoptotic properties against A375 human melanoma cells at 10  $\mu$ g/mL concentrations. On the other hand, celery extract abrogated the expansion of LPS-activated dendritic cells, the metabolic activity of which was attenuated by stimulation with celery extract. Stimulation of celery extract significantly reduced the anti-inflammatory IL-10 cytokine (Danciu et al., 2018). The activity of luteolin on other melanoma skin cancer is not found.

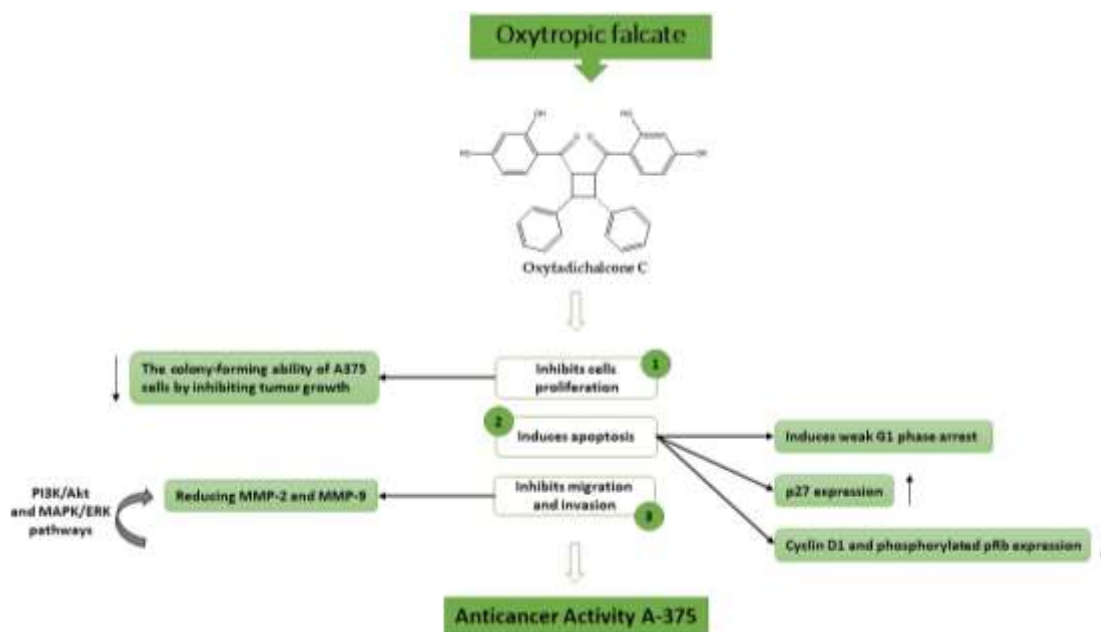


**Figure 9.** The mechanism of luteolin.

### 3.9. *Oxytropis falcata*

*Oxytropis falcata* Bunge (Leguminosae), known as "ErDa-Xia" in Tibetan medicine, is a wild plant that grows mainly in the Qinghai-Tibetan Plateau and has been empirically used to treat inflammation, wounds, and bleeding for thousands of years (Lin et al., 2017). Compounds isolated and identified from *O. falcata* include flavonoids, alkaloids, and saponins (Yan et al., 2009). Many studies reveal that flavonoids in *O. falcata* are the main active compounds responsible for the anti-inflammatory, antitumor, and antioxidant effects, as well as anti-cardiovascular disease (Jiang et al., 2009; Chen et al., 2010; Zhang et al., 2020b; Guo et al., 2022). The *O. falcata* extracts exhibit anticancer activity on various human cancer

cell lines, including prostate cancer, gastric cancer, and hepatocarcinoma. One of the compounds from *O. falcata*, which exhibits antitumor activity, is Oxyfadichalcone C (Figure 10) (Peng et al., 2018). Oxyfadichalcone C inhibits the A375 cells' proliferation with an IC<sub>50</sub> of 12.98 μM. It also decreases the colony-forming ability of A375 cells by inhibiting tumor growth (Peng et al., 2018). It induces weak G1 phase arrest and apoptosis in A375 cells by increasing p27 expression and decreasing cyclin D1 and phosphorylated pRb expression. Oxyfadichalcone C also inhibits the migration and invasion of A375 cells by reducing MMP-2 and MMP-9 through PI3K/Akt and MAPK/ERK pathways (Peng et al., 2018). The activity of oxyfadichalcone on other melanoma skin cancer is not found.



**Figure 10.** The mechanism of Oxyfadichalcone C.

### 3.10. *Erigeron breviscapus* (Vant) Hand. Mazz.

*Erigeron breviscapus* (vant.) Hand.Mazz. (EBHM) is a plant species endemic to southwest China and is a traditional Chinese herb used to treat various diseases, such as heart disease, cerebral infarction, digestive disorders, and apoplexy (Zhu et al., 2018). It contains scutellarin (Figure 11), which is flavone glucuronide (5,6,4'-trihydroxyflavone-7-O-glucuronide) (Zhu et al., 2018; Li et al., 2019). Scutellarin significantly inhibits melanoma cell line A375 viability. It also showed an antimigration effect and an anti-invasion effect. Scutellarin suppresses the adhesion of A375 cells drastically by increasing the E-cadherin expression and decreasing N-cadherin expression. In addition, it also decreases the MMP-2 and MMP-9 expression through the PI3K/Akt/mTOR signaling pathway in A375 cells (Li et al., 2019). MTS and soft agar assays detected the effect of Scutellarin on RPMI7951 cells. TOPK knockdown is caused by lentiviral infection. TOPK downstream signaling pathway was detected by western blot and in vitro immunohistochemical analysis. Scutellarin binds directly to TOPK and inhibits TOPK activity in vitro, inhibiting the proliferation and colony formation of RPMI7951 cells. Scutellarin inhibited

phosphorylation levels of Extracellular Regulatory Kinase 1/2 (ERK1/2) protein and histone H3 in RPMI7951 cells. In addition, Scutellarin inhibited the growth of tumor cell xenograft RPMI7951 (Mu et al., 2021).

### 3.11. *Camellia sinensis* (L.) O. Kuntze

*Camellia sinensis* belongs to Theaceae, an evergreen angiosperm dicot plant species whose leaves and leaf buds are native to mainland China and South and Southeast Asia. It is known as tea, the most consumed beverage in the world after water (Agarwal et al., 2017). It is widely used by all peoples of India and China and is popular in various indigenous systems of medicine, such as Ayurveda, Unani, and Homeopathy. All ages consume green tea in India, China, Japan, and Thailand (Agarwal et al., 2017). Green tea has been found to have various pharmacological activities such as anti-Alzheimer's, antioxidant, anti-parkinsonism, anti-stroke, anti-cardiovascular disease, anticancer, antidiabetic, anti-caries, anti-obesity, anti-aging, eye disease, antibacterial, anti-allergic, anti-hair loss, anti-inflammatory due to the presence of various chemical constituents (de Pascual et al., 2000; Armoskaite et al., 2011; Agarwal et al., 2017) such as polyphenols (catechins, theaflavins), theanine, and caffeine (Tai et al., 2015).

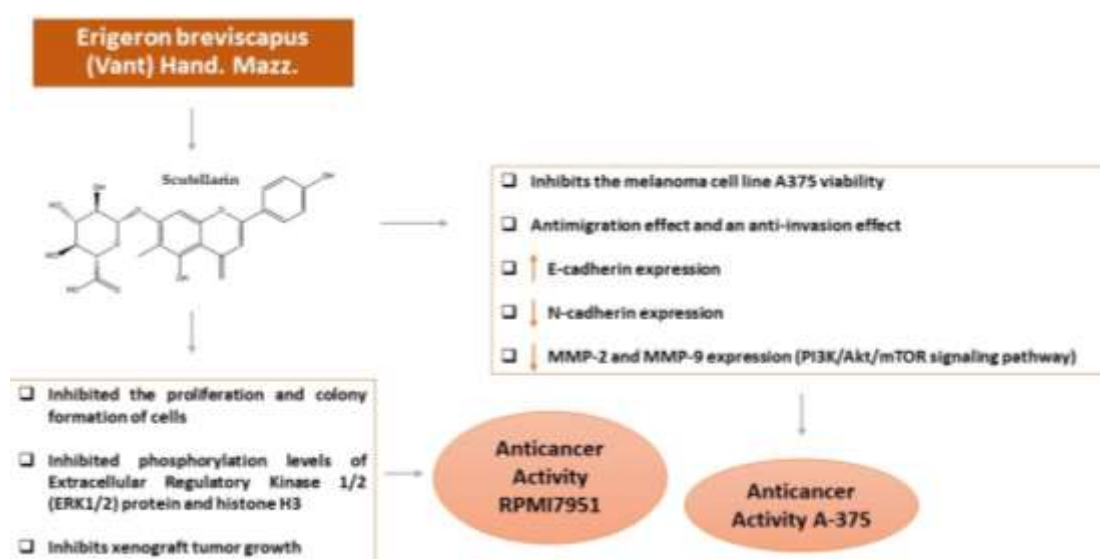
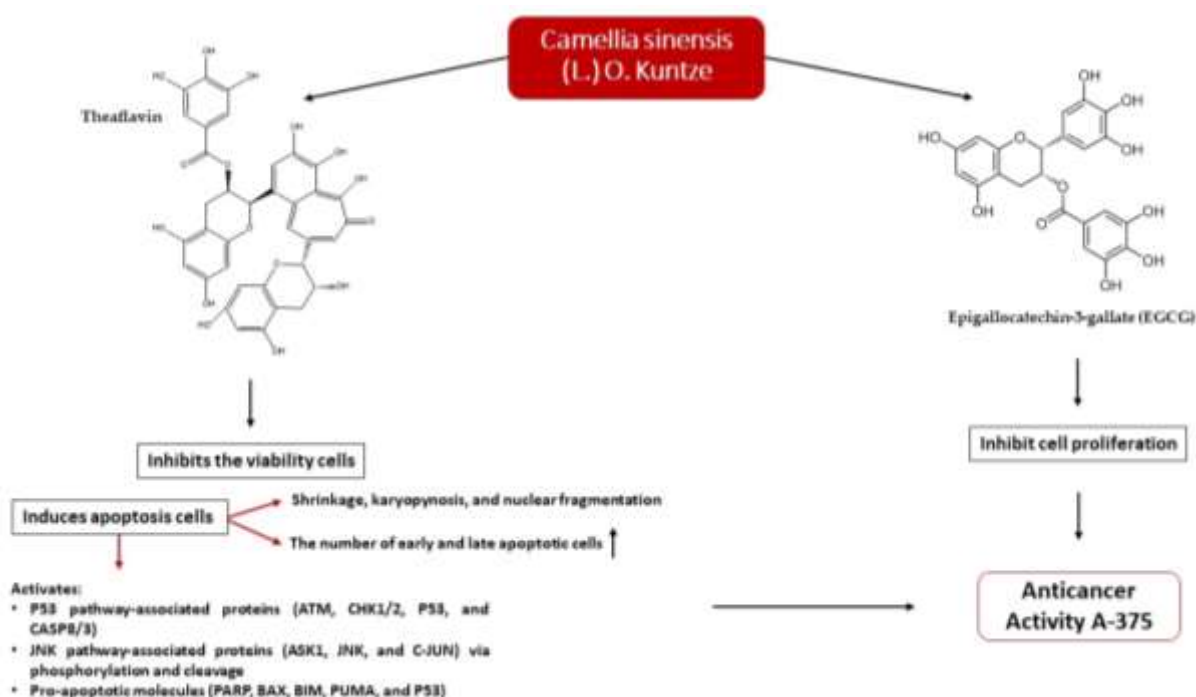


Figure 11. The mechanism of scutellarin.

Theaflavin/ TF (**Figure 12**) is a polyphenol produced from catechin oxidation during fermentation. It has anticancer activity by inducing apoptosis in various cancer cell lines, including human breast carcinoma cell lines (MCF-7, MDA-MB-231, T47D, and ZR-75-1), colon carcinoma cell lines (HCT-15 and HT-29), and liver carcinoma cell lines (HCCLM3 and Huh-7) (Zhang et al., 2020c). TF significantly inhibits the viability of A375 cells in a dose-dependent manner. It also induces apoptosis in A375 cells by shrinkage, karyopynosis, and nuclear fragmentation in TF-treated A375 cells, and the number of early and late apoptotic cells increased. TF significantly activates P53 pathway-associated proteins (ATM, CHK1/2, P53, and CASP8/3) and JNK pathway-associated proteins (ASK1, JNK, and C-JUN) via phosphorylation and cleavage, followed by activation of proapoptotic molecules (PARP, BAX, BIM, PUMA, and P53) (Zhang et al., 2020c). Epigallocatechin-3-gallate (EGCG) is the primary catechin in green tea. Nanovehicles for EGCG delivery (EGCG delivery) can effectively increase antioxidant

capacity, absorption, and bioavailability in vivo. In this study, thermally modified lactoglobulin (-Lg), 3-mercapto-1-hexanol (3MH), and EGCG were used to form stable co-assembled nanocomplexes (ME-NPs) with more excellent stability, sustained release, and anticancer effects in vitro and in vivo than EGCG alone. ME-NPs inhibited the proliferation of tumor cells A375, Hep G2, and TE-1 with 65.90%, 60.44%, and 32.88% greater activity, respectively, than EGCG using the MTT method. ME-NPs were non-toxic to mice and inhibited the growth of A375 human melanoma cell tumor by 57.78%, twice as effective as EGCG alone. Thus, ME-NPs have more excellent stability and antitumor activity than EGCG, with potential value for anticancer therapy (Yang et al., 2017). Five tea extracts (green tea, black tea, oolong tea 861, oolong tea 732, and jasmine green tea) at 10 µg/ml and 50 µg/ml exhibited cytotoxic potential in human melanoma cells A375 that were analyzed using the MTT method (Chen et al., 2018). The activity of TF on other melanoma skin cancer has not been found yet.



**Figure 12.** The mechanism of theaflavin.

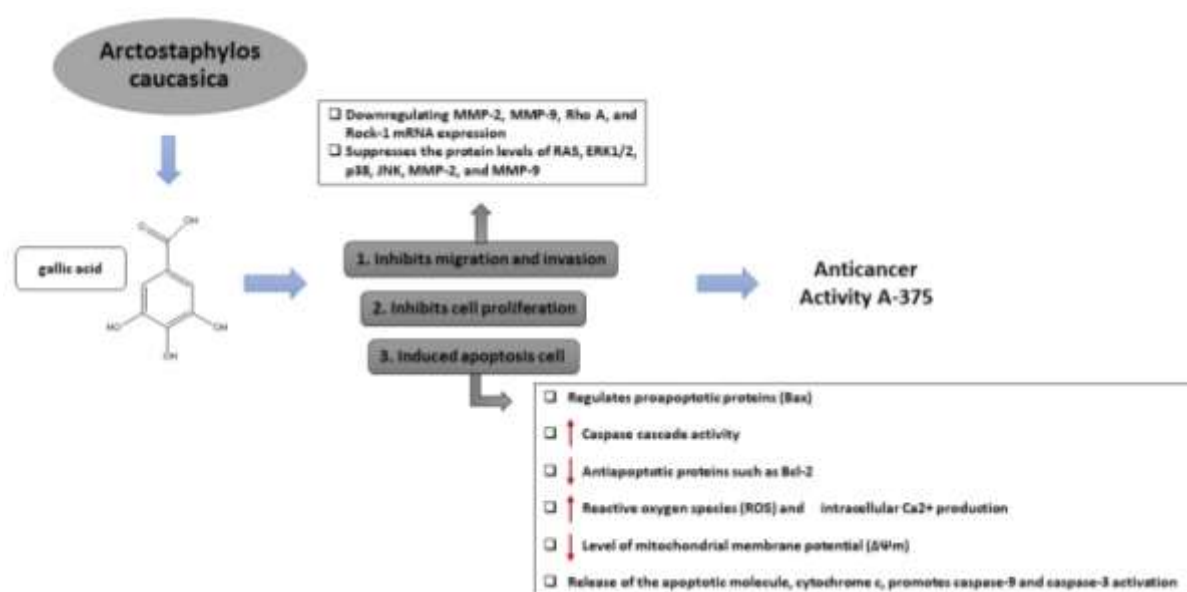


### 3.12. *Arctostaphylos Caucasica*

*Arctostaphylos caucasica* or Bearberry belongs to the genus *Arctostaphylos*. In various countries, It is known as Bearberry (UK), busserole (France), Bärentraube (Germany), oreja de oso (Spain), uva ursina (Italy) (Shamilov et al., 2021). It contains phenolic glycosides and flavonoids, including anthocyanins, hydroxycinnamic acid saponins, lignans, iridoids, polysaccharides, and essential oils in bearberry stems and leaves (Shamilov et al., 2021). Bearberry leaves and stems are mainly used as diuretics and antiseptics. Leaves of *Arctostaphylos caucasica* can also have anthelmintic, astringent, sedative, hemostatic, tonic, and metabolic effects (Abisheva et al., 2021). Several studies have shown that extracts from bearberry leaves have various pharmacological activities, including antibacterial, diuretic, nephrotic, antioxidant, antiproliferative, depigmentation, anti-inflammatory, antidiabetic, and neuroprotective (Shamilov et al., 2021). Gallic acid (3,4,5-trihydroxy benzoic acid, GA) (Figure 13) contained in Bearberry provides broad pharmacological activity such as antibacterial, antifungal, and antimalarial, antioxidant, and antiherpetic. It induces apoptosis in several cell lines and

inhibits the growth of human cancer cells in vitro and in vivo (Lo et al., 2011). GA inhibits the A375 cell line proliferation and migration of invasion. It decreases MMP expression, signal pathway proteins, and MMP mRNA in A375.S2 melanoma cells by downregulating MMP-2, MMP-9, Rho A, and Rock-1 mRNA expression in A375.S2 cells, which is related to the antimetastatic effect of GA. It also suppresses the protein levels of RAS, ERK1/2, p38, JNK, MMP-2, and MMP-9 in A375.S2 cells (Lo et al., 2011).

In addition, GA (Gallic Acid) affects morphological changes, regulates proapoptotic proteins such as Bax, and induces caspase cascade activity, but decreases antiapoptotic proteins such as Bcl-2. GA induces reactive oxygen species (ROS) and intracellular Ca<sup>2+</sup> production and decreases the level of mitochondrial membrane potential ( $\Delta\Psi_m$ ) in A375.S2 cells]. GA triggers the cytosolic release of the apoptotic molecule, cytochrome c, promotes caspase-9 and caspase-3 activation, and ultimately apoptotic cell death. In addition, GA also promotes the cytosolic release of apoptosis-inducing factor (AIF) and endonuclease G (Endo G) (Lo et al., 2010). The activity of GA on other melanoma skin cancer and in vivo assays was not found during the literature research.



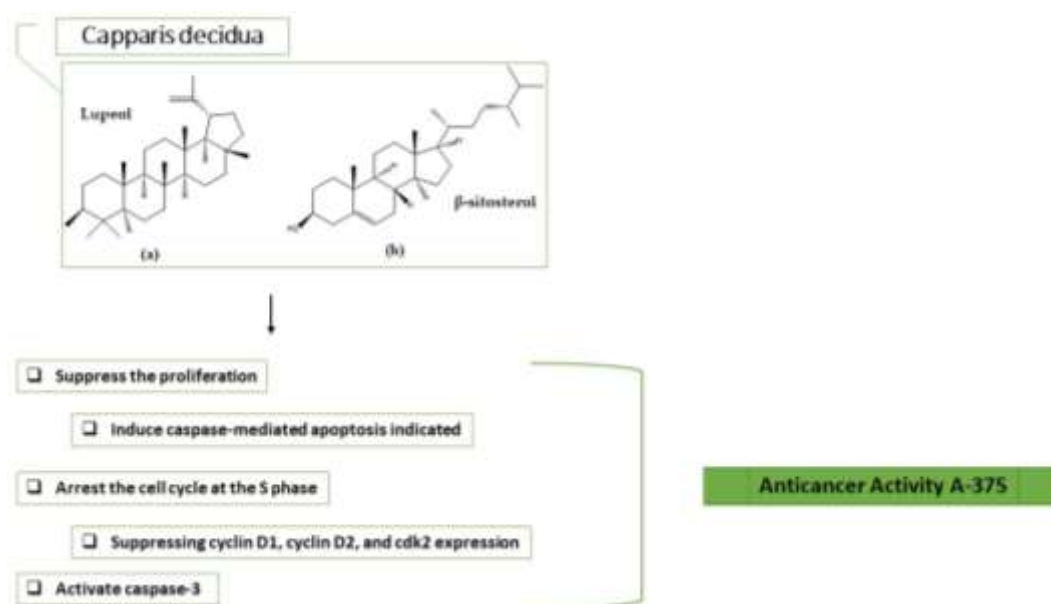
**Figure 13.** The mechanism of gallic acid.

### 3.13. Capparis Decidua

*Capparis decidua* belongs to the Capparidaceae family, originating from Pakistan, west India, and South Iran (Gupta, 2010; Naraghi et al., 2012; Gull et al., 2015). It also can be found in sub-tropical and tropical areas. It is commonly known as Kari, Delha, Caper, Kair, Karyal, Hanbag, Karil, and Kabra (Gupta, 2010). Empirically, it is efficacious for treating various diseases such as rheumatism, asthma, cough, backache, toothache, dengue fever, dysentery, liver infection, diarrhea, fever-reducing medicine, heart problems, constipation, ulcers, hemorrhoids, kidney disorders, and other skin diseases (Singh and Singh, 2011; Zia-Ul-Haq et al., 2011; Mann et al., 2013). It contains alkaloids (capparisinine), phenol hydroxybenzoic acid, flavonoids (isorhamnetin), sterols, terpenes, glycosides, and capparises terpenolides (Nazar et al., 2020). It has broad pharmacological activities such as antidepressant (Central Nervous System), anticonvulsant, hypolipidemic, antimicrobial, antihypertensive, antidiabetic, analgesic, antiplatelet, hepatoprotective, antioxidant activity, and cytotoxic activity against prostate cancer cells (Nazar et al., 2020; Shahraki et al., 2020).

Lupeol and  $\beta$ -sitosterol (Figure 14) are compounds in *C. decidua* with anticancer activity (Nazar et al., 2020; Shahraki et al., 2020). Hexane and chloroform extracts from *C. decidua* suppress the proliferation of A375 cells at relatively low concentrations (GI<sub>50</sub> = 10 and 18  $\mu$ g/mL, respectively), with an increase in cells with low DNA content (sub-G1). They induce caspase-mediated apoptosis with a high percentage of early and late apoptosis populations due to phosphatidylserine translocation to the outer membrane of cells. They arrest the cell cycle at the S phase, suppressing cyclin D1, cyclin D2, and cdk2 expression. They also activate caspase 3, leading to PARP cleavage induction and triggering p21 protein expression (Alqathama et al., 2022).

In addition, Lupeol showed anticancer activity against the A375 cell line with an IC<sub>50</sub> value of  $66.59 \pm 2.20$   $\mu$ M, accompanied by decreased cell confluence (educated cell confluence) and apoptosis-specific nuclear features, reorganization of cytoskeletal components, and inhibited cell migration. In vivo, lupeol interferes with angiogenesis by reducing neovascularization formation (Bociort et al., 2021). The activity of *C. decidua* on other melanoma skin cancer is not explored yet.



**Figure 14.** The mechanism of: (a) Lupeol and (b)  $\beta$ -sitosterol.

### 3.14. Haplophyllum Tuberculatum

*Haplophyllum tuberculatum* belongs to the Rutaceae family, mainly found in central and eastern Asia (Raissi et al., 2016). It is locally known as Haza and has been used traditionally to treat malaria, asthma, kidney disease, and gynecological and intestinal disorders (Eissa et al., 2014; Hamdi et al., 2018a). It contains various secondary metabolites, such as alkaloids (tuberine), lignans (justicidin A and justicidin B), essential oils ( $\beta$ -caryophyllene), and flavonoids (Raissi et al., 2016). It has broad pharmacological activity, such as an antiinfection agent and anticancer (Hamdi et al., 2018a; Hamdi et al., 2018b; Mahmoud et al., 2020). It is also used to treat cancer, malaria, rheumatoid arthritis, headaches, and gynecological problems and as a treatment for the nervous system and infertility (Raissi et al., 2016).

Justicidin B in *H. tuberculatum* (GI50 = 1.70  $\mu$ M) caused an increase in early and late

apoptotic populations. Cell cycle arrest induced in the S phase and morphological indicators of apoptosis (blebbing, apoptotic bodies, and nuclear fragmentation) accompanied by elevation of cells with low DNA content (sub-G1). In addition, Justicidin B increased the ratio of Bax/Bcl-2 by increasing the expression of Bax, which proves the involvement of mitochondria (intrinsic pathway) in the process of apoptosis and triggers the activation of caspase-3/7 (AlQathama et al., 2022).

The chloroform extract of *H. tuberculatum* (0.45  $\mu$ g/ml) is cytotoxic to A375 cell lines, associated with cell cycle arrest at the S phase. In addition, it induces apoptosis and causes nuclear fragmentation by activating caspase 3/7. It is due to justicidin A and justicidin B (Figure 15) contained in chloroform extract of *H. tuberculatum*, which have anticancer activity (AlQathama et al., 2022). The activity of *H. tuberculatum* on other melanoma skin cancer is not explored yet.

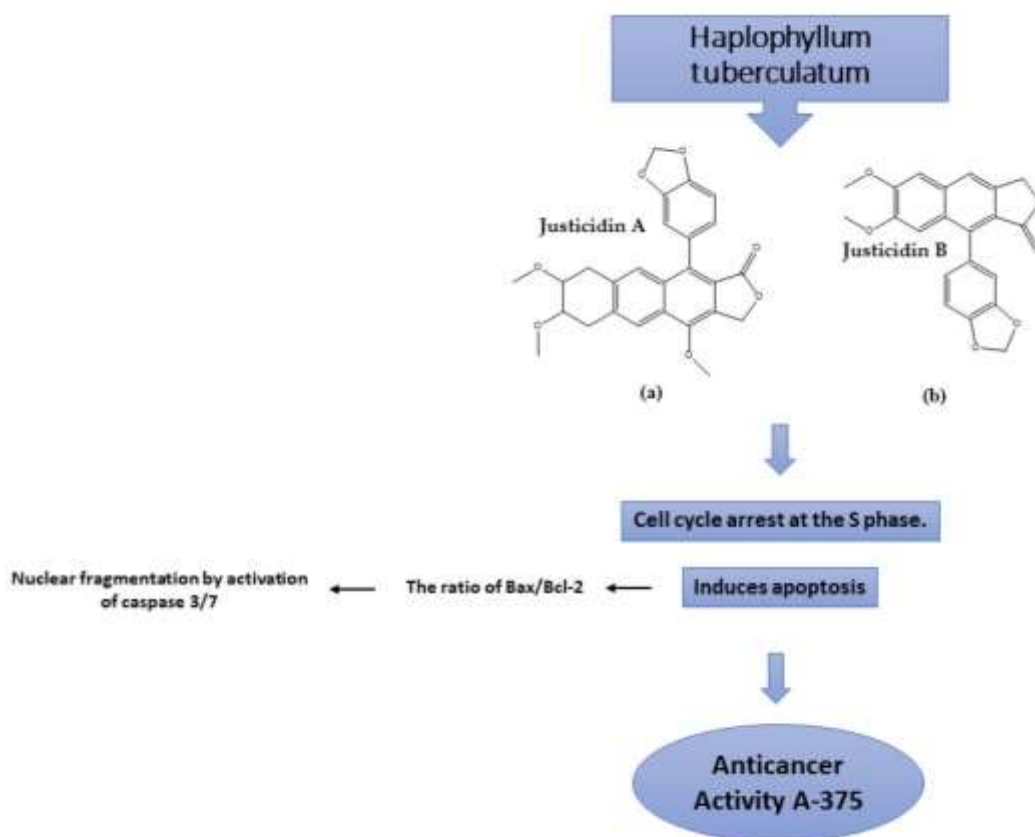


Figure 15. The mechanism of (a) Justicidin A dan (b) Justicidin B.

### 3.15. *Carissa Edulis*

*Carissa edulis* belongs to the Apocynaceae family and is mainly found from Arabia to Africa to the Transvaal, Botswana, and northern and northeastern Namibia, in grasslands and scrublands. It is traditionally utilized for treating tumors, epilepsy, malaria, pyrosis with stomach ulcers, arthritis, fever, hernias, and headaches (Ngulde et al., 2020). *C. edulis* contains flavonoid compounds, phenolic compounds, chlorogenic acid derivatives, lignans, and sesquiterpenes (Wangteeraprasert & Yawuid, 2009).

In pharmacological studies, *C. edulis* showed antiviral activity (Tolo et al., 2006) anticonvulsant (Yaro et al., 2008; Jawaid et al., 2011), antiplasmodial (Kirira et al., 2006), antimicrobial (Ibrahim et al., 1999), analgesic (Ibrahim et al., 2007), diuretic (Nedi et al., 2004), and hypoglycemic activity (El-Fiky et al., 1996). In addition, it contains ursolic acid, ursolic acid acetate, and quercetin (Figure 16), which act against A375 cell lines (Al-Youssef & Hassan, 2014).

Ursolic acid and ursolic acetate from hexane and chloroform extract of *C. edulis* inhibit the proliferation cell of A375 at a concentration of 15 µg/ml. They also arrest the cell cycle at the S phase through caspase 3/7 activation, indicated by the elevation of population percentage at early and late apoptotic.

The quercetin in the extract might synergize with both compounds in anticancer activity against A375 cell lines (AlQathama et al., 2022). Similarly, quercetin inhibits cell proliferation through the downregulation of signaling pathway proteins Wnt/β-catenin, DVL2, catenin, cyclin D1, Cox2, and Axin2. In addition, quercetin induces apoptosis by downregulating BCL2 and triggering caspase 3/7 via PARP cleavage (Srivastava & Srivastava, 2018).

In addition, ursolic acid at concentrations of 50 and 75 µM decreased cell viability after 24 h (80%) and was more pronounced after 48 h (47%) (Sass et al., 2012). The activity of

this extract on other melanoma skin cancer and in vivo are not explored yet.

### 3.16. *Artemisia L.*

*Artemisia L.* belongs to Anthemideae and consists of more than 500 species widely found in Asia, Europe, and North America (Abad et al., 2012). Empirically, it has been used for treating several diseases such as cancer, malaria, hepatitis, inflammation, and fungal, bacterial, and viral infections. It has various secondary metabolites such as essential oils, saponins, flavonoids, cyanogenic glycosides, phenols, tannins, phenolic glycosides, unsaturated lactones, and glucosinolates (Hussain et al., 2017).

Eupatilin/ 5,7-dihydroxy-3',4', 6-trimethoxyflavone (Figure 17) is a flavonoid compound isolated from the *Artemisia* plant (Shawi et al., 2011). Eupatilin at concentrations 0-800 µM inhibits the A375 cell growth by inducing apoptosis by causing morphological changes, including chromatin condensation, cell differentiation, nuclear fragmentation, apoptotic body formation, and DNA fragmentation. It also induces cell cycle arrest at the G2/M phase and decreases the cell population in the G1/G0 phase of the cell cycle in A375 cells (Shawi et al., 2016).

Sesquiterpene lactone fraction derived from the plant *Artemisia khorassanica* selectively inhibited melanoma cell proliferation by inducing apoptosis and overexpression of Bax and cytochrome c (Rabe et al., 2015). The results showed that EOs (Essential oils) were very active in melanoma cancer cells (IC50 values 6.7 and 4.5 µg/mL), induced apoptosis which disrupted endogenous defense mechanisms, increased ROS production in cells, and induced GSH depletion in cells. melanoma (Russo et al., 2020).

*Artemisia L.* extract significantly inhibited α-MSH-induced melanogenesis and tyrosinase activity. Western blot showed that *Artemisia* Extract downregulated the expression of melanocyte-specific proteins such as tyrosinase, protein tyrosinase-1 (TRP-

1), and protein tyrosinase-2, which catalyzes the rate oxidation of tyrosine to melanin, inhibits melanin pigment synthesis and tyrosinase activity in B16F10 melanoma cells.

(Woo et al., 2019). The activity of eupatilin against other melanoma skin cancer has not been explored yet.

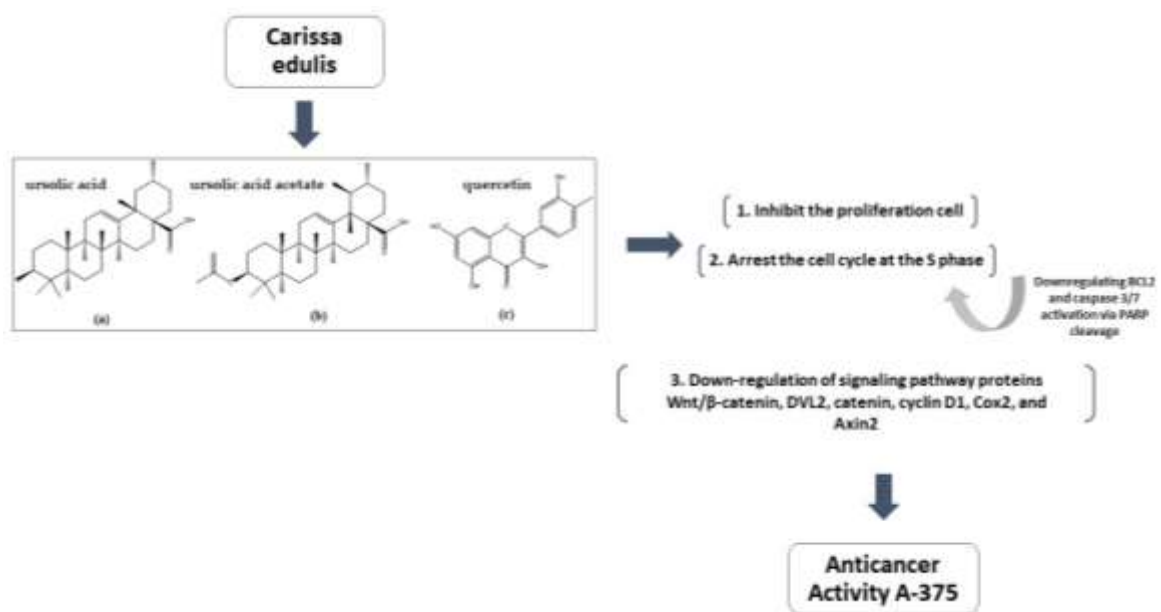


Figure 16. The mechanism of (a) ursolic acid; (b) ursolic acid acetate; and (c) quercetin.

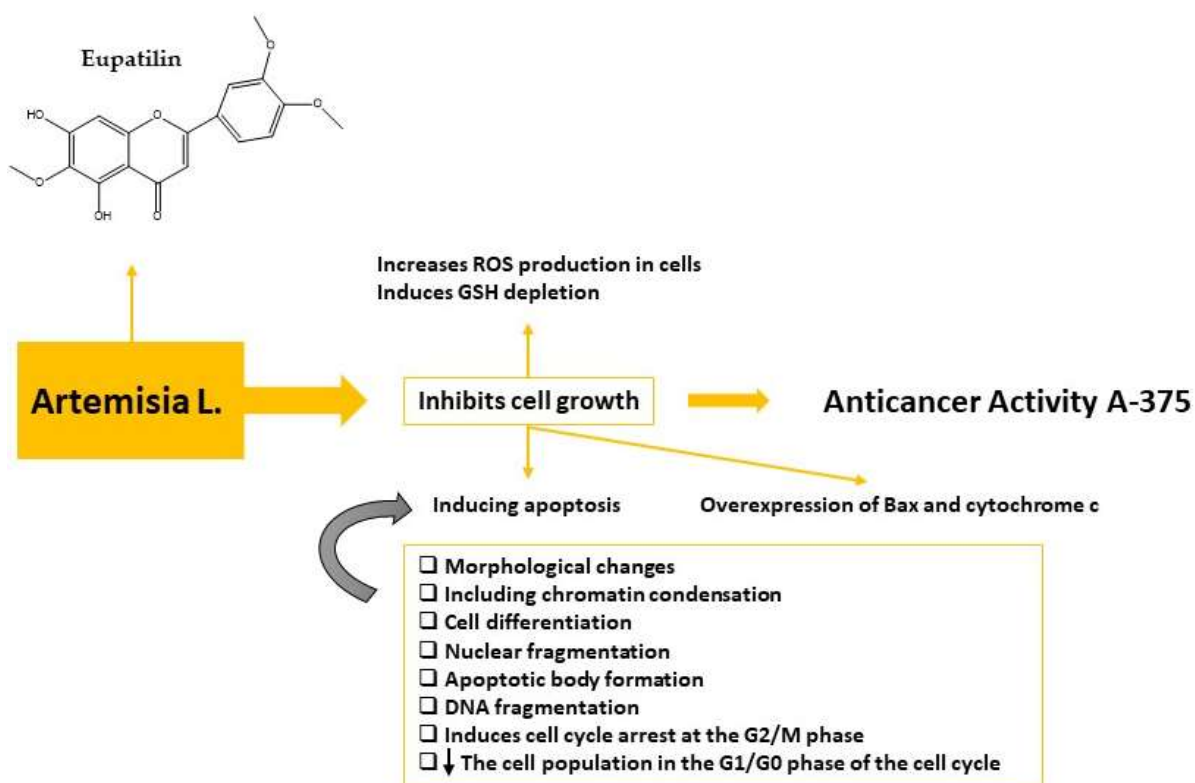


Figure 17. The mechanism of eupatilin.

### 3.17. *Pinus Maritima*

*Pinus maritima* (PM) grows in the tropics in Thailand and has been widely used as a traditional Thai topical and oral medicine to treat various ailments. PM can also be found in some Western European countries, such as Portugal, Spain, France, and some North African countries (Chupin et al., 2015). It has various pharmacological effects, including anti-inflammatory, antioxidant, anticarcinogenic, antimutagenic, antifertility, antibacterial, and antifungal activities (Dhippayom et al., 2015). PM has beneficial phenolic compounds, with procyanidin oligomers as the predominant phenolics. Typical phenolic compounds in PM are catechins, epicatechins, dihydroquercetin, and phenolic acids (Figure 18) (Vieito et al., 2018).

PM extract has anticancer activity against A375 cell lines by triggering apoptosis through increased cell ROS production. Reactive Oxygen Species (ROS) are reactive molecules and free radicals derived from molecular oxygen, by-products of mitochondrial electron transport of aerobic respiration or oxidoreductase, and metal-catalyzed oxidation enzymes. It will activate p21 to trigger apoptotic (Tong et al., 2015; Thaichinda et al., 2018).

Pine bark extract (PBE) on human A375 malignant melanoma cells showed that PBE (5 µg/mL) induced apoptosis and inhibited cell migration and invasion. Caspase-3 expression and activity were significantly increased in PBE-treated cells. PBE improves the formation of reactive oxygen species (ROS) induced by hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>). Treatment of cells with PBE led to a significant reduction in matrix metalloproteinase 9, which is the mediator responsible for advanced melanoma. PBE induces A375 apoptosis and suppresses cellular invasion by attenuating pathways in ROS associated with MMP-9 reduction (Thaichinda et al., 2018). Treatment of A375 cells with catechins resulted in inhibition of cell migration or cell invasion, with decreased levels of cyclooxygenase receptors (COX)-2, prostaglandins (PG) E<sub>2</sub>, and PGE<sub>2</sub> (EP<sub>2</sub> and EP<sub>4</sub>). In addition, catechins inhibited the activation of NF-κB/p65, a COX-2 regulator, in A375 melanoma cells. There was an increase in the levels of epithelial biomarkers (E-cadherin, cytokeratin, and desmoglein 2) and a decrease in the levels of mesenchymal biomarkers (vimentin), fibronectin, and N-cadherin in A375 melanoma cells (Singh & Santosh, 2011). The activity of PM extracts on other melanoma skin cancer and in vivo studies is limited.

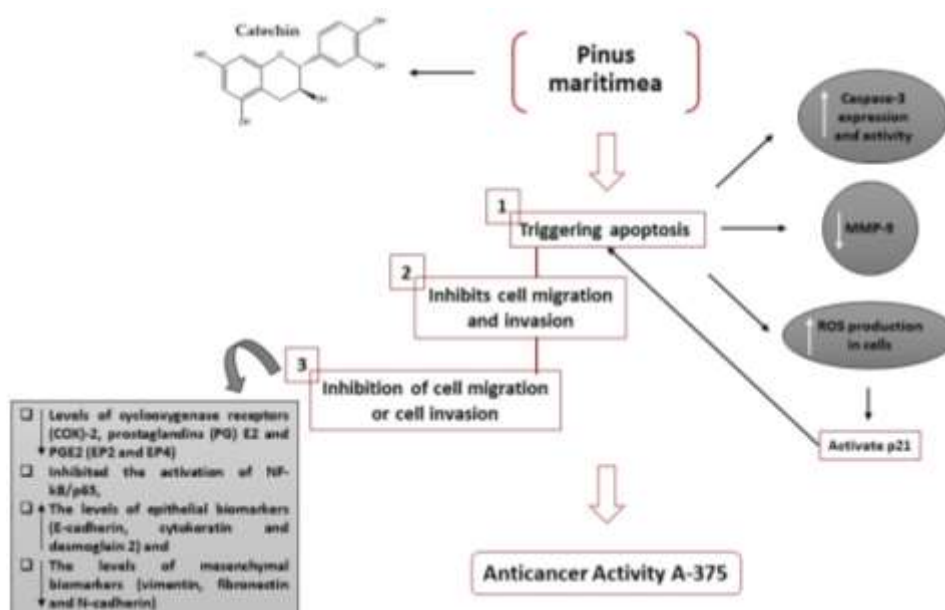


Figure 18. The mechanism of catechin.

### 3.18. *Andrographis paniculata*

*Andrographis paniculata* belongs to the Acanthaceae family, widely known for its bitter taste. It is an annual, branched, erect, tall herb running half to one meter in height. It is native to peninsular India and Srilanka and distributed in Southeast Asia, China, America, West Indies, and the Christmas Island regions. The aerial parts and roots of the plant have been widely used as traditional medicine in China, India, Thailand, and other Southeast Asian countries to treat many maladies (Okhuarobo et al., 2014).

*A. paniculata* is used empirically to treat colds, diarrhea, and fever. It is also used for treating leprosy, leptospirosis, malaria, rabies, upper respiratory infections, sinusitis, syphilis, tuberculosis, and HIV/AIDS (Kumar et al., 2021; Sa-Ngiasuntorn et al., 2021). Phytochemical studies have revealed that *A. paniculata* contains diterpenoid lactones (34.95%) and flavonoids (46.23%) are the major classes of chemical compounds, primarily from aerial parts (61.93%). Other classes, such as terpenoids (10.22%), phenolic acids (4.30%), chalconoids (2.15%), xanthenes (2.15%), and volatile compounds also reported in different plant parts (Okhuarobo et al., 2014; Kumar et al., 2021).

The main bioactive component of *A. paniculata* is andrographolide (Figure 19) (Sa-Ngiasuntorn et al., 2021). Andrographolide has been formulated into nanoemulsions and tested for its anticancer activity. The result showed a cytotoxicity effect on human melanoma cells (A375) through induction of apoptosis with high selectivity index and inhibited intracellular tyrosinase activity in A375 cells (Asasutjarit et al., 2021). In addition, andrographolide potentially inhibited cell proliferation by inducing G2/M cell cycle arrest and decreasing the proportion of cells in the G0/G1 and S phases in C8161 and A375 cell lines. The treatment of andrographolide against C8161 and A375 cell lines induces

apoptosis. It is associated with the cleavage of poly (adenosine diphosphate-ribose) polymerase and activation of caspase-3. It was observed that andrographolide induces activation of the c-Jun N-terminal kinase and p38 signaling pathways, which may be associated with cell cycle arrest and apoptosis (Liu and Chu, 2018).

Treatment of APE and ANDLE significantly reduced these elevated levels. Moreover, the VEGF mRNA level in the B16F-10 cell line showed a reduced expression level in the presence of *Andrographis paniculata* extract (APE) and its major component, andrographolide (ANDLE). Serum NO level was increased in B16F-10 melanoma injected control animals, and it was also found to be significantly lowered by the administration of APE and ANDLE. Antiangiogenic factors such as TIMP-1 and IL-2 levels were elevated in APE and ANDLE-treated angiogenesis-induced animals (Sheeja et al., 2007).

Andrographolide was evaluated in vivo using xenograft/syngeneic tumor models. Andrographolide inhibited the growth rate of B16 melanoma tumors in immunocompetent C57BL/6 mice and HT-29 tumors in nude mice without body weight loss and clinical symptoms of toxicity. Andrographolide inhibited the in vivo growth of B16 melanoma and HT-29 cells with similar potency (Rajagopal et al., 2003). In B16 cells and mouse models, andrographolide inhibited melanoma tumor growth and metastasis by inducing cell cycle arrest and apoptosis. In addition, Andro significantly inhibited the TLR4/NF- $\kappa$ B signaling pathway. Furthermore, the inactivation of TLR4/NF- $\kappa$ B signaling inhibited the mRNA and protein expression of CXCR4 and Bcl-6, antitumor genes (Zhang et al., 2014). Andrographolide also induces apoptosis *via* inhibiting NF- $\kappa$ B-induced Bcl-2-mediated survival signaling and modulating p53-induced caspase-3-mediated proapoptotic signaling in B16F-10 melanoma cells (Pratheeshkumar et al., 2012).

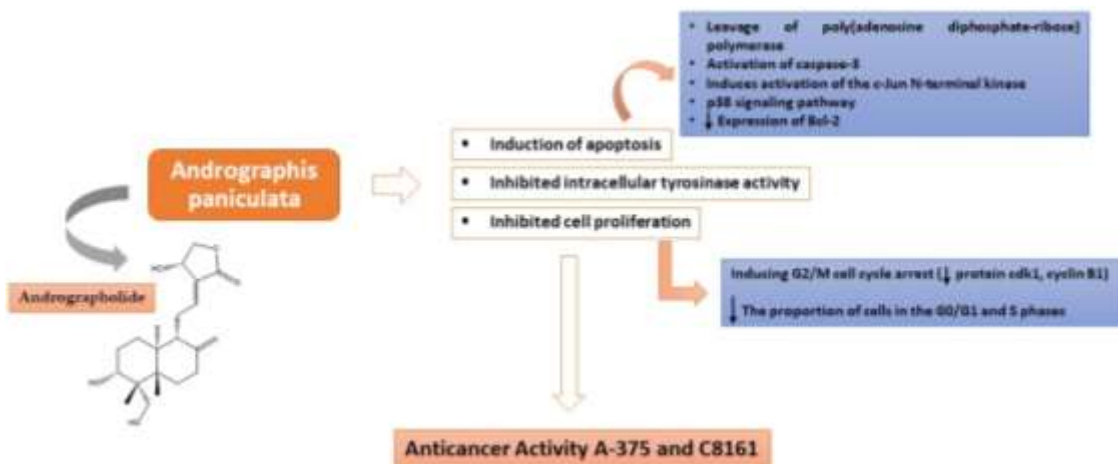


Figure 19. The mechanism of andrographolide.

### 3.19. Vitex Rotundifolia L.

*Vitex rotundifolia* L. fruit is mainly found in rural China, Taiwan, and Korea and is traditionally used to treat gastroenteritis, inflammation, and headaches. Casticin is one of the compounds with anticancer activity (Figure 20), one of the active ingredients derived from Fructus Viticis. Previous studies show that casticin suppresses A375 cell proliferation and antimetastatic potential by reducing A375 cell invasion. Several studies have found that casticin can downregulate the migration and invasiveness of A375 cells through the p-EGFR/Ras/p-ERK pathway. Casticin significantly binds NF-κB p65 to the NF-κB p65 promoter, also decreases levels of NF-κB p65 and NF-κB proteins (p50) and

increases IκB levels in A375 (Shiue et al., 2016; Wu et al., 2016). In addition, casticin also decreased the expression of p-ERK 1/2, p-MEK 1/2, p-c-jun, p-EGFR, and MMP-1 in A375 cells (Wu et al., 2016). Casticin also induces changes in cell morphology and damage to cell DNA and can induce G2/M phase arrest and apoptosis. In addition, casticin induces apoptosis with mitochondrial dysfunction, then causes cytochrome c followed by activating caspase-9 and -3 in A375 cells. Casticin exhibits the expression of proapoptotic proteins such as Bax and Bak and decreases the expression of antiapoptotic proteins such as Bcl-2, Bcl-xl, Mcl-1, and x-IAP (Shiue et al., 2016). The activity of casticin on other melanoma skin cancer is limited.

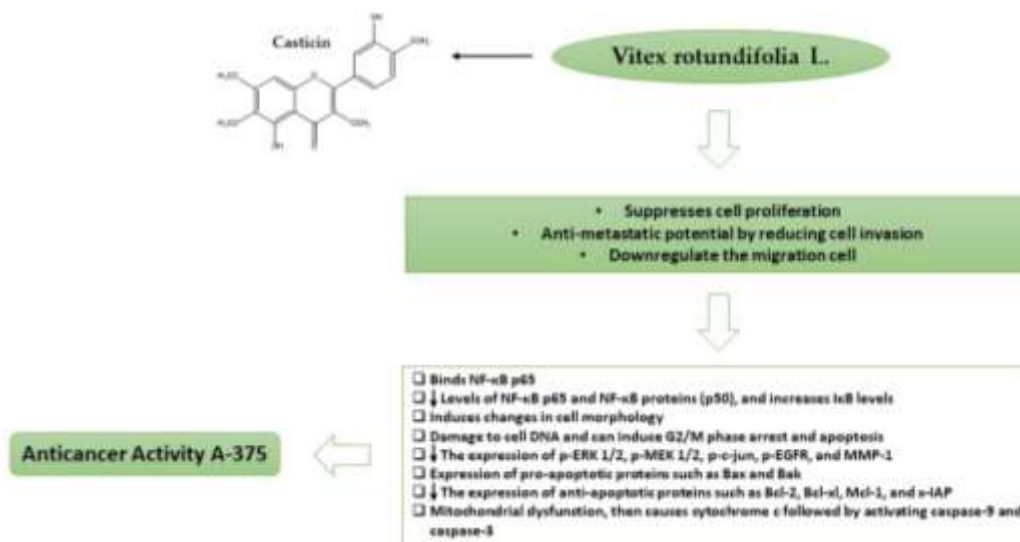


Figure 20. The mechanism of Casticin.



### 3.20. Galenia Africana

*Galenia Africana*, also known as 'kraalbos' or 'geelbos,' is a medicinal plant widely distributed in South Africa and is mainly found in Namaqualand and the West and South Karoo. *G. africana* is used empirically to treat coughs, wounds, tuberculosis, skin infections, and eye inflammation.

*G. africana* has been used traditionally in the form of pastes, decoctions, and lotions to treat wounds and other skin-related ailments (Ndlovu et al., 2021; Heredia et al., 2022). The bioassay-guided fractionation of the EtOH extract of the leaves of *Galenia africana* led to the isolation of three known flavonoids, (2S)-5,7,2'-trihydroxyflavanone, (E)-3,2',4'-trihydroxychalcone, and (E)-2',4'-dihydroxychalcone, and the new (E)-3,2',4'-trihydroxy-3'-methoxychalcone (Mativandlela et al., 2009).

*G. africana* contains flavonoids which provide various biochemical properties and health benefits. One of them is 5,7-dihydroxyflavone (pinocembrin) (Figure 21). *G. africana* significantly reduced A375 cell viability depending on time and dose. Meanwhile, it was also tested with normal cells, and the results did not affect HaCaT cells. A375 cells after treatment showed nuclear condensation, brightly colored nuclei, and nuclear fragmentation, indicating apoptosis (Ndlovu et al., 2021).

In vivo, pinocembrin inhibited the growth of B16F10 by inducing apoptosis. Pinocembrin suppressed autophagy by activating the PI3K/Akt/mTOR pathway, which serves as a dual mechanism to enhance the pro-death effect of pinocembrin (Zheng et al., 2018). The activity of *G. Africana* extract against other melanoma skin cancer is limited.

### 3.21. Selaginella P. Beauv

*Selaginella P. Beauv.* is the only extant genus in the family Selaginellaceae. It is mainly found in tropical and subtropical areas around the world. Extracts of the plant *Selaginella tamariscina* (P. Beauv.) Spring

(spike moss) has been used for a long time in Asia for the treatment of multiple diseases and conditions in aqueous and alcoholic leaf extracts.

The plant (Juan bai) in China is listed on Pharmacopoeia. In South Korea, it (Kwon Baek) is mentioned in the book Dongui-Bogam (Heo Jun 1613) as the origin of the Hyungsang medicine. *S. tamariscina* is traditionally used in Vietnam (mong lung rong), Thailand (dok hin), Philippines (pakong-tulog) and other Asian countries (Bailly et al., 2021). Due to their pharmacological activity, several species of *Selaginella* have been used extensively for treating inflammation, dysmenorrhea, chronic hepatitis, and hyperglycemia (Křížková et al., 2021).

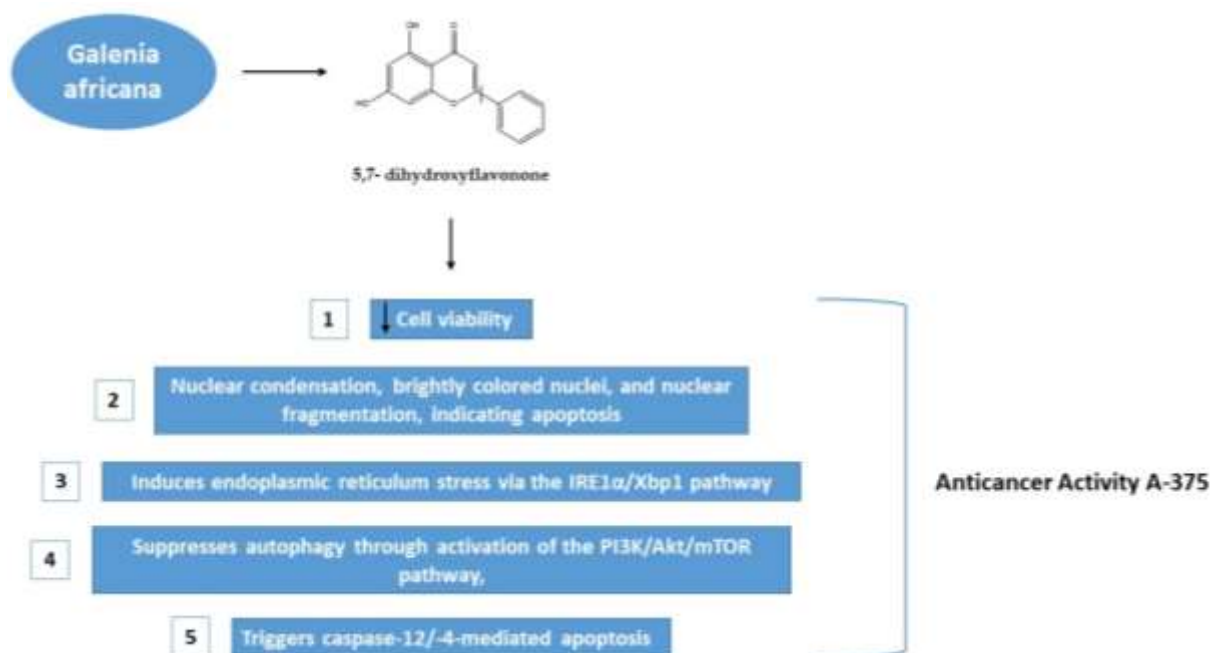
*Selaginella P. Beauv* contains hinokiflavone, widely studied as an anticancer agent (Figure 22). Hinokiflavone inhibits the proliferation of A375 cells in both doses- and time-dependent manner. In addition, it inhibits the progression of the cell cycle in the S phase, depending on the concentration.

Hinokiflavone also induces apoptosis associated with caspase-3 activation, down-regulation of Bcl-2, and up-regulation of Bax expression. In addition, hinokiflavone increases reactive oxygen species (ROS) and decreases mitochondrial membrane potential. Furthermore, hinokiflavone effectively interfered with A375 cell migration and invasion and decreased the expression of matrix metalloproteinases (MMPs) MMP2, and MMP9 (Yang et al., 2018b).

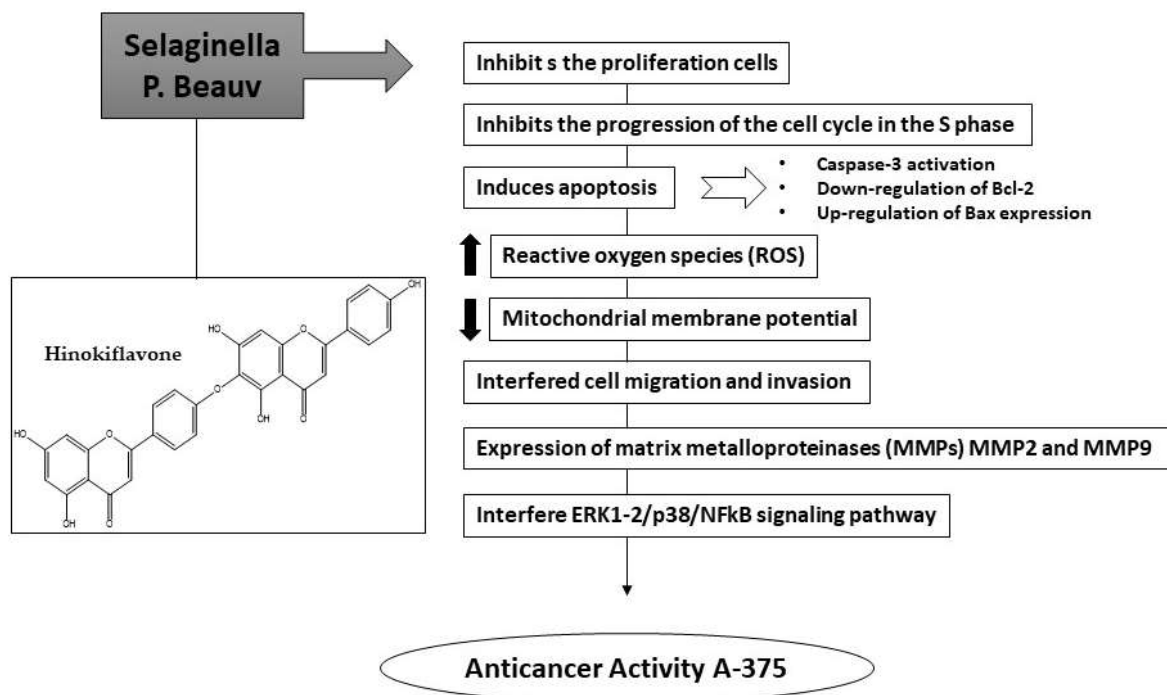
The anticancer activity of hinokiflavone is related to its capacity to interfere ERK1-2/p38/NFκB signaling pathway. In addition, hinokiflavone is a potent modulator of pre-mRNA splicing, inhibiting the SUMO-specific SENP1 protease. Thus, hinokiflavone represents a rare natural-derived SENP1 inhibitor and a scaffold for designing synthetic compounds (Goossens et al., 2021).

Other studies showed that hinokiflavone influences A-375 and B16 cell survival by inducing apoptosis and arresting the cell cycle progress at phase S in a concentration-

dependent manner (Francois et al., 2021). The activity of hinokiflavone on other melanoma skin cancer is not found during the literature researching



**Figure 21.** The mechanism of 5,7- dihydroxyflavonone.



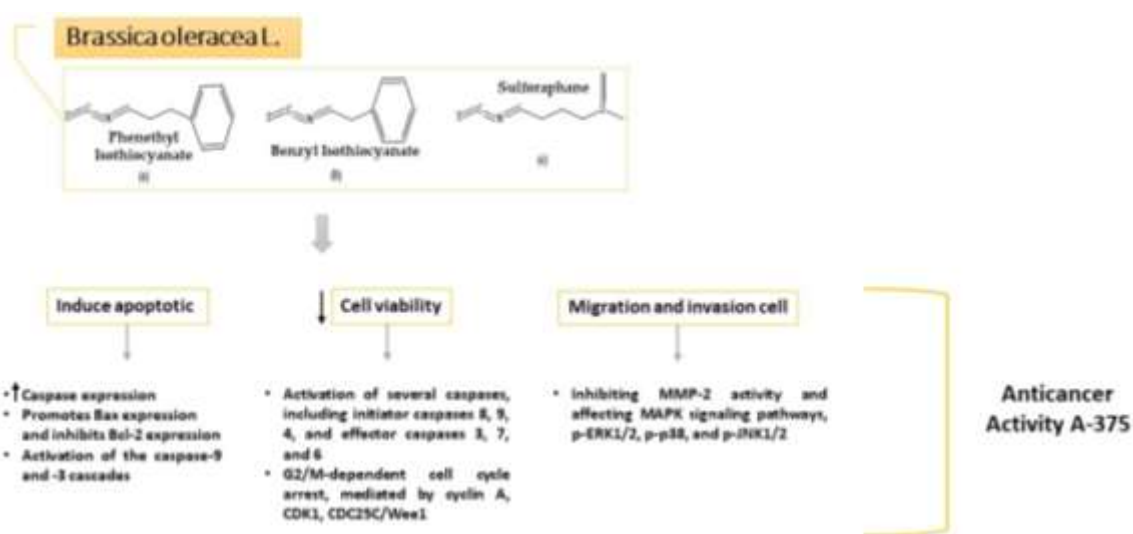
**Figure 22.** The mechanism of hinokiflavone.

### 3.22. Brassica Oleracea L.

*Brassica oleracea* L. (Brassicaceae) is mainly used as a food source like vegetables and traditional medicines (Lyles et al., 2021). It has been reported that consumption of *Brassica oleracea* L. has recently been associated with a reduced risk of cancer development. The isothiocyanates (ITC) and their derivatives (Phenethyl Isothiocyanate (PEITC), Benzyl Isothiocyanate (BITC), and Sulforaphane (SFN) contained in *Brassica oleracea* L. were reported to providing this effect (Figure 23). ITC induces higher ROS, leading to cycle arrest in the G2/M phase in A375 cell lines. It also induces necrotic cell death and apoptosis in metastatic melanoma cells (Mitsiogianni et al., 2021). In addition, ITC induces an accelerated antiangiogenic effect mediated by decreased levels of TNF- $\alpha$ , NO, and VEGF (Mitsiogianni et al., 2018).

SFN, BITC, and PEITC also showed a cytotoxic effect on the A375 cell line through several apoptotic pathways by increasing caspase expression (Mitsiogianni et al., 2018). Decreased cell viability involves the activation of several caspases, including initiator caspases 8, 9, and 4 and effector caspases 3, 7, and 6 (Mantso et al., 2016). A 5  $\mu$ M of SFN, BITC, and PEITC were upregulated to create a G2/M cycle by affecting cycling regulators of A375 cell lines.

In addition, PEITC at 5–15  $\mu$ M concentrations inhibited A375 cell growth by causing G2/M-dependent cell cycle arrest and inducing a ROS-mediated intrinsic apoptotic pathway (Mitsiogianni et al., 2019). PEITC induces alteration and inhibition of the G2/M phase and apoptosis through mitochondrial-dependent pathways mediated by endoplasmic reticulum stress. PEITC promotes Bax expression and inhibits Bcl-2 expression, associated with outer mitochondrial membrane disintegration leading to cytochrome c and activation of the caspase-9 and -3 cascades leading to apoptosis. It concludes that PEITC-induced apoptotic death in A375 cells occurs via a ROS-mediated mitochondrial-dependent pathway (Huang et al., 2014). BITC increases ROS accumulation in cells and causes altered expression of various cyclins and CDKs (e.g., cyclin A, CDK1, CDC25), proteins from the B-cell lymphoma family 2 (BCL2), and various caspases (Mitsiogianni et al., 2019). Another study showed that BITC and PEITC also prevented A375 cell migration and invasion by inhibiting MMP-2 activity and affecting MAPK signaling pathways, including p-ERK1/2, p-p38, and p-JNK1/2 (Ma et al., 2017; Mitsiogianni et al., 2019). In contrast, the activity against other melanoma skin cancer cell lines is limited.



**Figure 23.** The mechanism of (a) Phenethyl Isothiocyanate, (b) Benzyl Isothiocyanate, and (c) Sulforaphane.

### 3.23. Rosmarinus Officinalis L.

Rosemary (*Rosmarinus officinalis* L.) belongs to the Lamiaceae family and has been widely used in the Mediterranean region since ancient times as a culinary spice to preserve food or enhance its taste in cooking. Rosemary contains Rosmarinic acid, Apigenin, Scutellarin, and Carnosic Acid (Figure 24). This plant has drawn more attention due to its several biological activities, including antihyperglycemic (Bao et al., 2020), antibacterial, anticancer, antioxidant, antithrombotic (Bourhia et al., 2019), memory boosting (Ghasemzadeh et al., 2020), anti-inflammatory (de Melo et al., 2011), and hepatoprotective effects (Abdel-Wahhab et al., 2011).

The results showed that *R. officinalis* extract could decrease the viability of A375 cells through the induction of apoptosis and cell cycle arrest at sub-G0, G0/G1, and G2/M phases (Russo et al., 2009; Cells et al., 2015). In addition, the methanolic extract of *R. officinalis* can resist nitric oxide-mediated plasmid DNA damage, which is beneficial in preventing UV-R-related cellular damage, including dermatitis, premature aging, and skin cancer (Cattaneo et al., 2015).

The extract showed a protective effect on plasmid DNA damage at 10-80 µg/mL concentrations. It was able to reduce significantly ( $p < 0.001$ ) the growth (MTT assay) of both melanoma cell lines. In addition, it also induced apoptosis in M14 and A375 cells (Russo et al., 2009). However, the activity against other melanoma skin cancer cell lines is limited.

### 3.24. Sanguinaria Canadensis

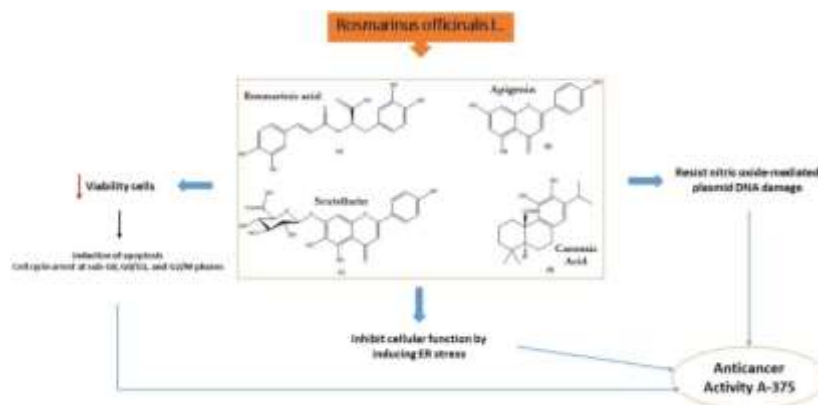
*Sanguinaria canadensis* is a North American herbaceous plant whose rhizome is famous as a bloodroot due to its red sap. The rhizome contains alkaloids, such as

sanguinarine, chelerythrine, sanguilutine, chelilutine, sanguirubine, chelirubine, and two protopin alkaloids protopine and allocryptopine (Croaker et al., 2016; Tuzimski et al., 2021), which provide antimicrobial (Miao et al., 2011), cardiovascular, neuroreceptor, anti-inflammatory, and anticancer activities (Figure 25).

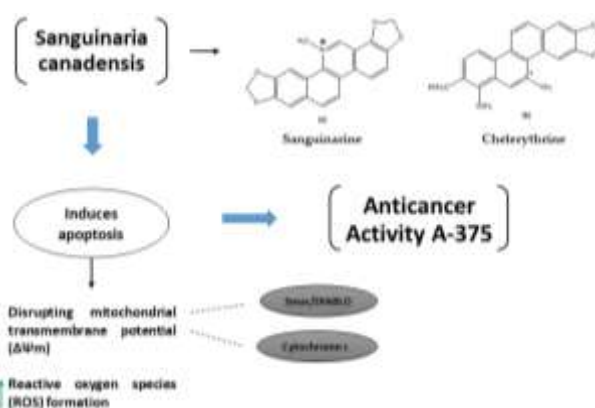
*S. canadensis* has high antiproliferative activity against A375 cells with  $IC_{50}$  0.88 to 10.96 µg/mL (Tuzimski et al., 2021). In addition, the sanguinarine induces apoptosis by disrupting mitochondrial transmembrane potential ( $\Delta\Psi_m$ ). Thus, it releases cytochrome c and Smac/DIABLO from mitochondria to cytosol. In addition, it increases reactive oxygen species (ROS) formation (Burgeiro et al., 2013).

In vitro cytotoxic activity of sanguinarine and chelerythrine was obtained against B16 melanoma 4A5 cells, a cell line derived from subcutaneously inoculated B16F0 tumors in the C57BL/6 strain mouse, and human melanoma A375 cells. Antiproliferative effects of isoquinoline alkaloids—sanguinarine, chelerythrine, chelidonine, sanguilutine, and chelilutine were investigated on malignant melanoma A-375 and SK-MEL-2 cell lines. Cytotoxicity of sanguinarine was also investigated in mouse melanoma K1735-M cell lines (Serafim et al., 2008; Hammerova et al., 2011).

In the present study, we investigated in vitro cytotoxic activities of isoquinoline alkaloids standards and plant extracts obtained from *Sanguinaria canadensis*, collected before, during, and after flowering, using human Caucasian malignant melanoma cell line (G361) and human malignant melanoma cell line (SKMEL3) (Tuzimski et al., 2021). The activity of this extract against other melanoma skin cancer cell lines is limited.



**Figure 24.** The mechanism of (a) Rosmarinic acid, (b) Apigenin, (c) Scutellarin, and (d) Carnosic Acid.



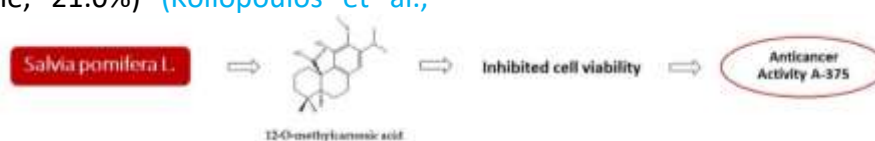
**Figure 25.** The mechanism of (a) sanguinarine and (b) chelerythrine.

### 3.25. *Salvia pomifera* L.

*Salvia pomifera* L. belongs to the Lamiaceae family, an Eastern Mediterranean element distributed in Greece and the Aegean coasts of Turkey (Leontaritou et al., 2021). In China, about 40 *Salvia* species have been used as medicinal plants to treat various diseases, specifically hepatic and renal diseases, and those of the cardiovascular and immune systems (Xu et al., 2018). The volatile metabolites of wild-growing *S. pomifera* subsp. *pomifera* from Greece were determined by gas chromatography and gas chromatography-mass spectrometry. *S. pomifera* subsp. *pomifera* (trans-caryophyllene, 22.5% and trans-thujone, 21.0%) (Koliopoulos et al.,

2010). *Salvia* species are sources of health-promoting phytochemicals that comprise polyphenols, flavonoids, terpenes, and several other constituents. Many studies have indicated that plants from the *Salvia* genus reduce oxidative stress and may be able to prevent and treat inflammatory diseases (Bonesi et al., 2017).

It contains 12-O-methylcarnosic acid, inhibiting cell viability and proliferation (Figure 25). Methanolic extract of *S. pomifera* inhibited cell viability with an IC<sub>50</sub> value of 70.29 μg/mL on the A375 cell line. In contrast, it is not providing apoptosis in cell cycle arrest (Koutsoulas et al., 2019). However, the activity against other melanoma skin cancer is limited.



**Figure 26.** The mechanism of 12-O-methylcarnosic acid.

### 3.26. *Salvia Fruticosa* Mill.

*S. fruticosa* is an endemic plant found in the Mediterranean and Irano-Turania areas, with Carnosic acid being the most potent active compound for anticancer (Figure 27). *Salvia* species have been traditionally used to improve cognition and proved to be a potential natural treatment for Alzheimer's disease. It is also known as Greek sage, and has been reported to exert significant antioxidant, and anticancer activity (Sevindik et al., 2014; Boukhary et al., 2016), anticholinergic (Gürbüz et al., 2021). The effects of *Salvia* extracts and carnosic acid, the main diterpene phenolic component of *S. fruticosa*, on the proliferation and cell cycle of two melanoma cell lines (A375, Mel JuSo) and human fibroblast cell line (HFF) were investigated by MTT assay, PI-exclusion assay, and flow cytometry cell cycle analysis.

*S. fruticosa* extract significantly reduces the proliferation of human melanoma cells. Carnosic acid affects microtubule dynamics and arrests the cell cycle in the G2/M phase (Koutsoulas et al., 2019). In addition, *S. fruticosa* extract is the most potent in reducing the cell viability level of A375 cells with an IC<sub>50</sub> value of 0.048 mg/mL at 48 hours. Similarly, it is safe for normal cells by not showing any cytotoxic effect on HaCat

cells. In addition, it induces apoptosis by activating the extrinsic apoptotic pathway through Caspase-8 activation. It also involves an intrinsic apoptotic pathway through caspase-9 activation (Kyriakou et al., 2021). Especially in melanoma cells, previous studies have shown that CA seems to block cell migration of B16F10, an aggressive melanoma cell line, by inhibiting epithelial-mesenchymal transition (EMT). This inhibition subsequently resulted in anoikis activation, a form of apoptosis (Park et al., 2014). In another study, CA activated the KEAP1/NRF2 axis inducing NQO1 expression. In this way, CA could enhance the toxicity of other anticancer drugs in melanoma treatment (Arakawa et al., 2018). Carnosic acid (CA) is another crucial diterpene phenolic compound in *S. fruticosa*, also known for its antioxidant and anti-inflammatory properties. Specifically, the treatment of melanoma cell lines with CA resulted in: the induction of apoptotic cell death; inhibition of epithelial-to-mesenchymal transition (EMT) and metastasis; as well as improvement of the cytotoxicity profile of several anticancer drugs (Arakawa et al., 2018; Koutsoulas et al., 2019). The activity of *S. fruticosa* extract against other melanoma skin cancer cell lines is not explored yet.

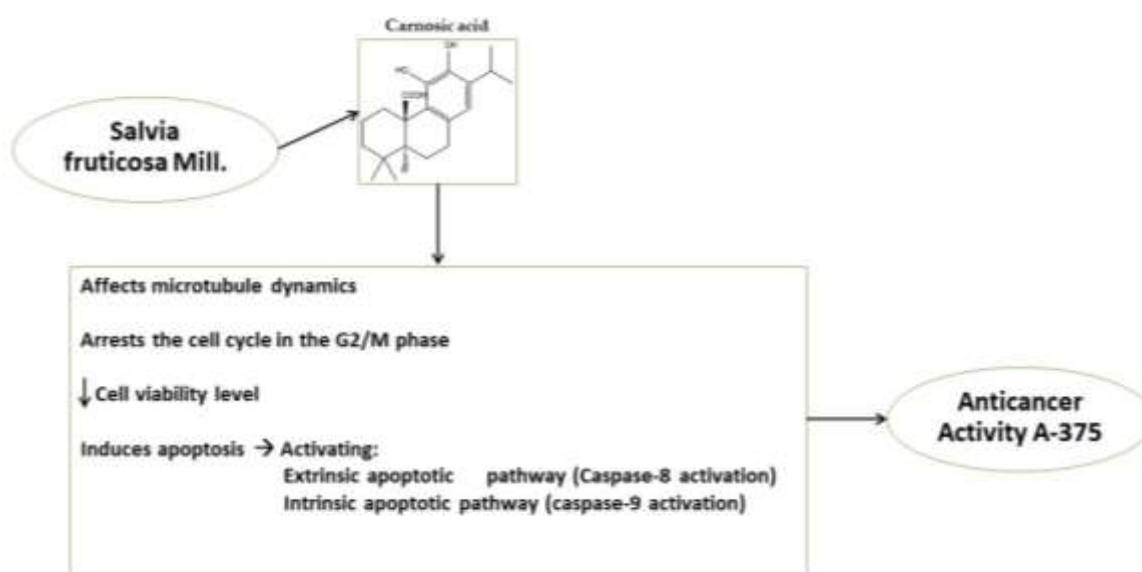


Figure 27. The mechanism of carnosic acid.

### 3.27. *Garcinia mangostana* L.

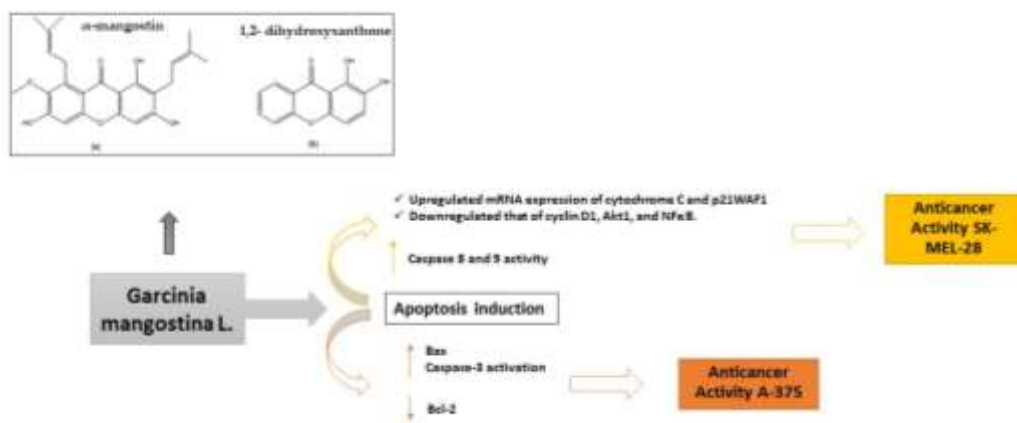
*Garcinia mangostana* L., or mangosteen, is a tropical evergreen tree native to Southeast Asia belonging to the Clusiaceae or Guttiferae family. Xanthenes are bioactive compounds from *G. mangostana*, which have tricyclic aromatic rings substituted with phenolic, methoxy, and isoprene groups (Maligan et al., 2019; Gunter et al., 2020). In this case, the xanthone derivative in the form of alpha-mangostin ( $\alpha$ M) is the main component (Maligan et al., 2019). The seeds and pericarp are mainly used empirically, including for treating gastrointestinal and urinary tract infections, laxatives, anti-fever agents, and treatment of insomnia (Abate et al., 2022). It has an activity as an antitumor, anti-inflammatory, and antioxidant.  $\alpha$ -mangostin and 1,2-dihydroxyxanthone are known for their anticancer activity (Figure 28).  $\alpha$ -mangostin inhibits cancer progression through apoptosis induction by increasing Bax, decreasing Bcl-2, and increasing caspase-3 activation (Gunter et al., 2020; Kurniawan et al., 2021). In addition, a marked decrease in adhesion and invasion of A375 cell adhesion (Marowicz et al., 2019). The 1,2-DHX inhibits the growth of A375-C5 cells, although the mechanism is unclear and requires further analysis (Silva et al., 2019). Another study showed  $\alpha$ -mangostin inhibited the proliferation, adhesion, and invasion of SK-MEL-28 and A375 cells in vitro (Gunter et al., 2020).  $\alpha$ -Mangostin (7.5  $\mu$ g/mL) activated caspase 8 and 9 activity, increasing 3-fold and 4-fold, respectively. The molecular mechanism was investigated by qRT-PCR, and the results showed  $\alpha$ -mangostin significantly increased cytochrome C and p21WAF1 mRNA expression and downregulated cyclin D1, Akt1, and NFkB. It suggests that xanthenes induce an inhibitory effect on SK-MEL-28 cells by modulating molecular targets involved in the apoptotic pathway (Wang et al., 2017).

### 3.28. *Citrus grandis* (Linn.) Osbeck

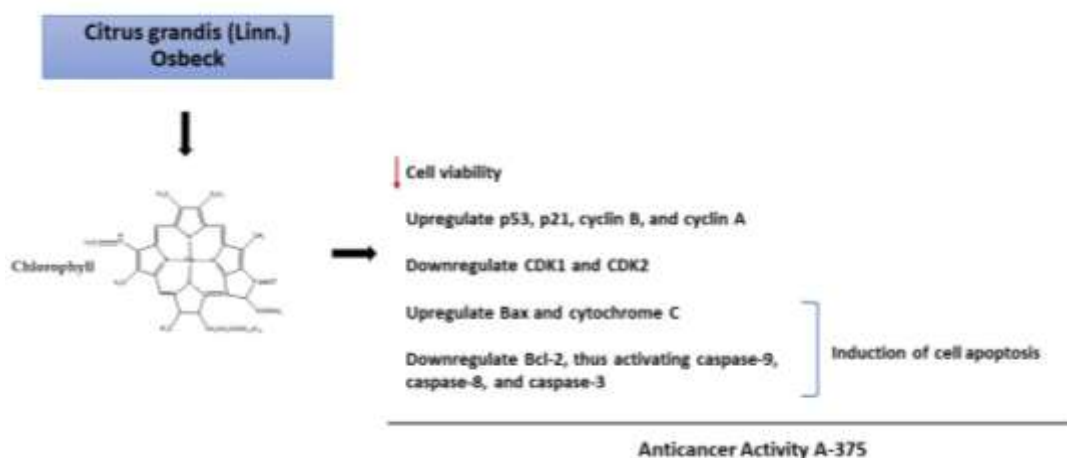
*Citrus grandis* (L.) Osbeck, commonly known as Pomelo, belongs to the family Rutaceae and is considered the significant ancestor of the grapefruit (Anmol et al., 2021). Red wendun is the local name for *C. grandis* in Taiwan. The essential oil of this species is used as a significant ingredient of flavor, the leaves are used as a food flavoring, and dried leaves are brewed in water as a drink. Red wendun leaves have long been used as herbal remedies in traditional Chinese medicine to promote blood circulation and remove blood stasis in diseases caused by blood stagnation (Rao et al., 2011).

In some Asian countries, the *C. grandis* fruits are not just used for consumption but also the other parts of this plant are practiced in folk culture such as leaves oil of *Citrus grandis* are applied to treat skin disorders, headaches, and abdominal pain (Tsai et al., 2017). Similarly, *C. grandis* flowers are used against anxiety and sleep disorders. Its fruits are used for mental abnormality, asthma, leprosy, hiccup, cough, and epilepsy (Duan et al., 2014).

*Citrus grandis* is rich in dietary fiber, vitamins, minerals, and phytochemicals, effectively preventing chronic disease. Chlorophyll and carotenoids from *C. grandis* are potential anticancer. Chlorophyll and carotenoid decrease cell viability and upregulate p53, p21, cyclin B, and cyclin A and downregulate CDK1 and CDK2 in a concentration-dependent manner for the inhibition of A375 cell lines. Furthermore, both nanoemulsions of chlorophyll and carotenoids upregulate Bax and cytochrome C and downregulate Bcl-2, thus activating caspase-9, caspase-8, and caspase-3 for the induction of cell apoptosis (Liu et al., 2021a; Liu et al., 2021b). The activity of compounds in *C. grandis* extract against other melanoma skin cancer is not explored yet.



**Figure 28.** The mechanism of (a)  $\alpha$ -mangostin and (b) 1,2- dihydroxyxanthone.



**Figure 29.** The mechanism of chlorophyll.

### 3.29. Lycopodium Clavatum

*Lycopodium clavatum* (LC) is one species belonging to the Lycopodiaceae family and is widely found in tropical, subtropical, and many European countries (**Figure 30**). It has been used traditionally for various diseases, such as stomach pain, fight rheumatic diseases, muscle pain, Alzheimer's disease, and others. The crude extract of LC contains alkaloids, including lycopodine. Lycopodine provides anticancer activity in HeLa cells by inhibiting HeLa proliferation by inducing apoptosis through caspase-3 activation (**Das et al., 2012**). It also contains vanillic acid, coumaric acid, ferulic acid, cinnamic acid, huperzine A, lycoflexine, Alpha-onocerin, and sporopollenin. Apigenin is also found in *Lycopodium clavatum* (**Banerjee et al., 2014**).

Apigenin isolated from LC significantly inhibits the proliferation of A375 cell lines. It

also significantly increases early and late apoptotic cells by increasing Bax expression and decreases Bcl-2 expression in A375 cell lines, thus increasing ROS accumulation. It also upregulates caspase 3, 9, and PARP expression and downregulates cyt c expression in the mitochondrial (**Das et al., 2012**).

The protein expression levels of Bcl-2 were decreased. In contrast, those of Bax, cleaved poly ADP-ribose polymerase, cleaved caspase-9, and p53 were upregulated in a dose-dependent manner in apigenin-treated cells compared with those noted in untreated cells. In addition, in apigenin-treated A375P cells, phosphorylated (p)-p38 was upregulated, and p-extracellular signal-regulated kinase (ERK), p-c-Jun N-terminal kinase (JNK), and p-protein kinase B (Akt) were



downregulated. However, in A375SM cells, apigenin treatment increased p-ERK and p-JNK and decreased p-p38 and p-Akt protein expression levels. In vivo, Tumor volume was significantly reduced in the 25 and 50 mg/kg apigenin-treated groups compared with the control group (Woo et al., 2020).

In melanoma model cells SK-MEL-24, Apigenin was shown to be involved in the inhibition of angiogenesis by suppressing VEGF and HIF-1 $\alpha$  expression, ERK1/2 inactivation, and STAT3 signaling, and decreased MMP-2 and MMP-9 expression levels. The results obtained in the SK-MEL-24 melanoma model using the chorioallantoic membrane assay came to emphasize that treatment with 30 and 60  $\mu$ M induced a reduction in neovascularization in addition to limiting the growth and migration of melanoma cells. Apigenin concentrations of 30 and 60  $\mu$ M reduced viability and migration of SK-MEL-24 melanoma cells and resulted in a slight change in melanoma cell morphology at 24 h post-stimulation. In addition, at the chorioallantoic membrane of tumors, apigenin decreases tumor cell development (Ghițu et al., 2021). Apigenin-7-glucoside exhibited significant antiproliferative activity against B16F10 melanoma cells after 24 and 48 h of incubation. Furthermore, apigenin-7-glucoside increased subG0/G1, S, and G2/M phase cell proportion with a significant decrease in cell proportion in G0/G1 phases. The results evaluated using Hoechst 33,258 confirm that the percentage of B16F10 cells observed in the sub G0/G1 phase were undergoing apoptosis. Moreover, apigenin-7-glucoside revealed an ability to enhance melanogenesis synthesis and tyrosinase activity of B16F10 melanoma cells (Nasr et al., 2015).

### 3.30. *Trametes Robiniophila* Murr

*Trametes robiniophila* Murr or Huaier has been used in traditional Chinese medicine (TCM) for over 1,600 years as aqueous extracts and granules (Pan et al., 2019). The main active ingredients in Huaier are

proteoglycans, consisting of polysaccharide-protein (PS-T), containing about 40% of polysaccharides, 10% of amino acids, six monosaccharides, and 18 amino acids (Lv et al., 2022) (Figure 31).

Huaier has clinical effects on nephrosis, colitis, tuberous sclerosis, and cancer. It also shows a potent anticancer effect (Pan et al., 2019). Huaier has been shown to inhibit the proliferation of melanoma cells and other solid tumors and promote tumor cell apoptosis and invasion, metastasis, and angiogenesis in many types of solid tumors, such as hepatocellular carcinoma and colorectal carcinoma. Huaier extract strongly inhibited cell proliferation of the A875 melanoma cells and induced G2/M arrest and apoptosis in a time- and dose-dependent manner. P53 expression was increased, and cell apoptosis was executed by caspase 3. Down-regulation of Bcl-2 and up-regulation of Bcl2-associated X protein (BAX) indicated that Huaier extracts induced apoptosis through the mitochondrial pathway. As expected, the inhibitor Huaier decreased melanoma cell line A875 proliferation and induced apoptosis in a time- and dose-dependent manner (Zhang et al., 2013; Song et al., 2015).

Huaier extract significantly inhibits A375 cell metastasis at concentrations ranging from 4-16 mg/ml, in vitro and in vivo. In addition, Huaier extract possesses an antimetastasis effect through HIF-1 $\alpha$ /VEGF and AEG-1 signaling pathways and inhibition of the epithelial-mesenchymal transition (EMT) by downregulating hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ), vascular endothelial growth factor (VEGF), astrocyte-elevated gene-1 (AEG-1), and N-cadherin expression, whereas upregulating E.-cadherin expression in A375 cells and tumor tissue (Su et al., 2020). The anticancer effect of Huaier extract has been confirmed in liver, lung, breast, ovarian, gastric, and prostate cancer (Yang et al., 2015; Liu et al., 2020). The activity of Huaier extract on other melanoma skin cancer is not explored yet.

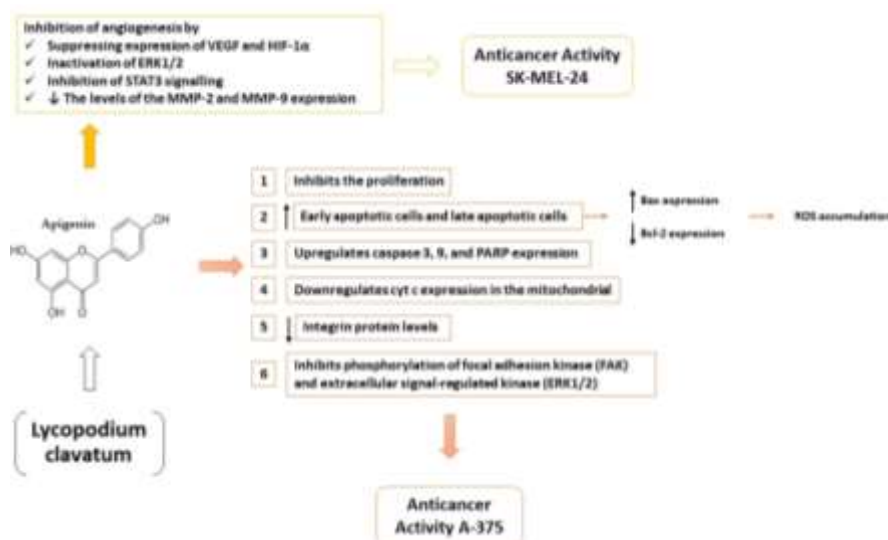


Figure 30. The mechanism of Apigenin.

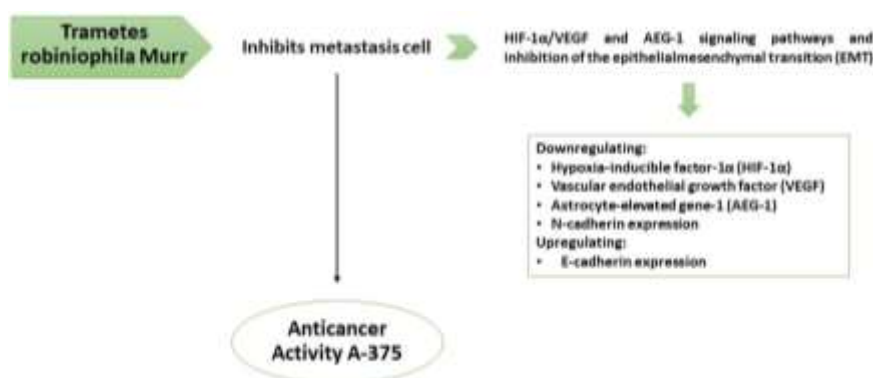


Figure 31. The mechanism of Huaier extract.

### 3.31. Scutellaria baicalensis

Plants from the genus *Scutellaria*, commonly known as skullcaps, are widely distributed in tropical temperate and mountainous regions, including Europe, North America, and East Asia. It has been used extensively in oriental medicine for thousands of years as traditional medicine. The genus *Scutellaria* provides antitumor, hepatoprotective, antioxidant, anti-inflammatory, anticonvulsant, antibacterial, and antiviral effects. One of *Scutellaria* is *S. baicalensis* which contains flavonoids, glycosides, and glucuronides. Besides flavonoids, *S. baicalensis* is also reported to contain phenylethanoid glycosides, iridoid glycosides, diterpenes, triterpenoids, alkaloids, and essential oils (Gaire et al., 2014). Wogonin is an O-methylated flavone, a flavonoid-like chemical compound isolated

from *S. baicalensis*. The glycosides of wogonin are known as wogonosides. Pharmacological effects indicate that wogonin has antitumor properties (Chen et al., 2017).

Methylwogonin induced a potent cytotoxic effect on human malignant melanoma cells A375, which IC<sub>50</sub> values of 72.9 and 54.2  $\mu$ M at 24 and 48 h, respectively (Figure 32). It inhibits colony formation in a dose-dependent manner of methylwogonin (Kurniawan et al., 2021). It also provides a proapoptotic effect by causing significant morphological changes, including chromatin condensation, fragmented nuclei, and cellular shrinkage. In addition, it also has an antimigration and anti-invasion effect through the mTOR/PI3K/AKT signaling pathway by downregulating PI3K, AKT, and phosphorylated mTOR in a dose-dependent manner (Chen et al., 2019b; He et al., 2021).

The activity compounds derivated from *S. baicalensis* have not been explored yet against other melanoma skin cancer.

### 3.32. Zingiber Officinale Roscoe

*Zingiber officinale* Roscoe, commonly known as ginger, belongs to the Zingiberaceae family and is a medicinal plant that has been widely used since antiquity in Chinese, Ayurvedic, and Unani herbal medicine throughout the world (McGee, 2004; Ali et al., 2008). Ginger cultivation originates from China and spreads to India, Southeast Asia, West Africa, and the Caribbean (McGee, 2004). Ginger is commonly used for various ailments such as arthritis, rheumatism, sprains, muscle aches, sore throats, cramps, constipation, indigestion, vomiting, hypertension, dementia, fever, infectious diseases, and helminthiasis (Ali et al., 2008; Shukla & Singh, 2007). In fresh ginger rhizome, gingerol was identified as the main active component (Hoffman, 2007). Ginger contains essential oils and non-volatile pungent compounds. The volatile oil components in ginger consist of sesquiterpene hydrocarbons, especially zingiberene (35%), curcumene (18%), and farnesene (10%) (Kumar Gupta and Sharma., 2014). Zerumbone (ZER) is a natural product isolated from the volatile essential oil of the plant *Zingiber officinale* Roscoe (Figure 33).

Several studies have shown that ZER has various biological activities, including antimicrobial, antioxidant, antidiabetic, anticancer, anti-inflammatory, antiallergenic, and antiangiogenic (Rahman et al., 2014).

Treatment of cells with *Zingiber officinale* Roscoe at concentrations of 0, 0.2, and 0.4 mg/mL for 24 hours significantly reduced cell viability. In addition, 70% ethanol extract of *Zingiber officinale* Roscoe showed antioxidant activity and inhibited the growth of A2058 cells, activating the mitochondrial apoptotic pathway of A2058 cells is mediated by modulating the expression of Bax and Bcl-2, which activates cleavage of caspases-3, caspases-9, and poly ADP-ribose polymerase (Guon et al., 2016). Whereas Oh et al. (2018) study showed that Zerumbone (ZER) at concentrations above 20  $\mu$ M exhibited a strong cytotoxic effect, ZER compounds significantly attenuated melanin accumulation in  $\alpha$ -melanocyte-stimulating hormone ( $\alpha$ -MSH), stimulating mouse melanogenic B16F10 cells. ZER inhibits MITF-mediated expression of melanogenic genes upon  $\alpha$ -MSH stimulation. In addition, cells treated with zerumbone concentrations showed increased extracellular signal-regulated phosphorylation of kinases 1 and 2 (ERK1/2), which are involved in MITF degradation mechanisms (Oh et al., 2018).

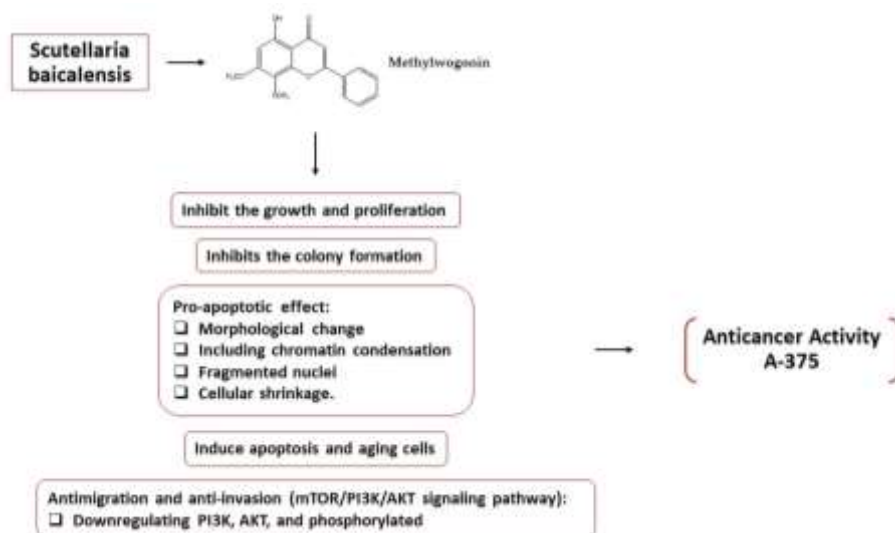


Figure 32. The mechanism of methyl wogonin.

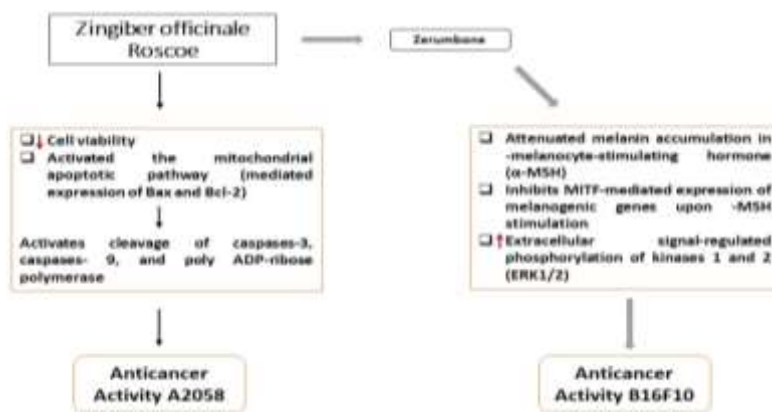


Figure 33. The mechanism of Zingiber officinale Roscoe.

### 3.33. Curcuma Longa

*Curcuma longa* L. (Zingiberaceae) grows naturally throughout the Indian subcontinent and in tropical countries, especially in Southeast Asia. Powdered extract of the dried rhizome of *C. longa*, often called turmeric, has been used as a spice in Indian and Asian cuisines and as a traditional medicine for thousands of years. *C. longa* contains three main curcuminoids: curcumin, demethoxycurcumin, and bisdemethoxycurcumin (Strimpakos & Sharma, 2008). The curcumin contained in *C. longa* has various antioxidant, anti-inflammatory, antidiabetic, hypolipidemic, anti-inflammatory, anti-diarrheal, hepatoprotective, anti-asthmatic, and anticancer properties (Tilak et al., 2004; Ali et al., 2006; Strimpakos & Sharma, 2008; Krup et al., 2013; Zhang et al., 2015).

Curcumin induced significant changes in the morphology of A375 cells. The number of A375 cells decreased significantly at concentrations of 12.5, 25, and 50 μM

( $p < 0.05$  or  $< 0.01$ ). Curcumin has antiproliferative and proapoptotic activity in A375 cells, which is related to the inhibition of the JAK-2/STAT-3 signaling pathway (Zhang et al., 2015). The methanol extract of *C. longa* rhizome was found to inhibit tyrosinase activity. After isolation using column chromatography and HPLC, eleven compounds (1 - 11) were identified in the rhizome of *C. longa* (Figure 34). The isolates were tested using an in vitro fungal tyrosinase test. The inhibition of melanin formation by the active compound was further evaluated using B16 mouse melanoma cells. Of the isolates, curcuminoids 5 – 7 (concentration 100 mg/mL) showed strong inhibitory activity in the tyrosinase test with IC50 values of 13.0, 11.3, and 10.9 μM, respectively. The formation of melanin from the active compound in B16 mouse melanoma cells is related to tyrosinase inhibitory activity, so the curcuminoids in the rhizome extract of *C. longa* help treat hyperpigmentation (Kim et al., 2008).

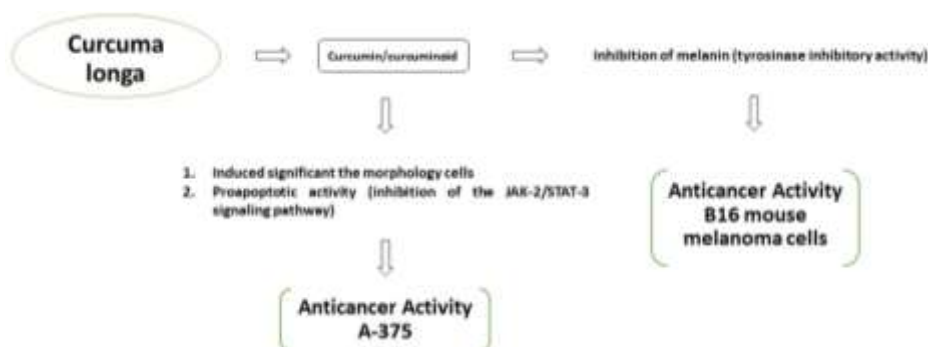


Figure 34. The mechanism of Curcuma longa L.

### 3.34. *Alpinia Galanga*

*Alpinia galanga* or known as galangal, which belongs to the Zingiberaceae family, grows mainly in Southeast Asia. It is now cultivated throughout tropical and subtropical Asia, such as India, Egypt, Thailand, Malaysia, Indonesia, and China (Padalia et al., 2010; Saeio et al., 2011; Yusoff et al., 2011). It is widely used in food and traditional medicine systems, namely traditional Ayurvedic, Unani, Chinese, and Thai medicine (Chouni & Paul, 2018). It is widely used as a food spice and local medicine in China and Thailand (Chudiwal et al., 2010), including microbial infections, inflammation, rheumatic pain, chest pain, dyspepsia, fever, burning of the liver, kidney disease, tumors, diabetes and even HIV (Ramesh et al., 2011).

*A. galanga* contains phenolic compounds, including flavonoids and phenolic acids. The dominant components isolated from the rhizome were galangoisoflavonoid, B-sitosterol diglucosyl caprate, and methyleugenol. p-coumaryl diacetate. 1'-acetoxyeugenol acetate, trans-p-acetoxycinnamyl alcohol, trans-3, 4-dimethoxycinnamyl alcohol, p-hydroxybenzaldehyde, p-hydroxycinamaldehyde, trans-p-coumaryl alcohol, galangin, trans-p-coumaric acid, and galanganol B (Kaushik et al., 2011). *A. galanga* rhizome has various activities, such as antioxidant, antifungal, antitumor, and anti-inflammatory activities (Lo et al., 2013).

Two compounds, 1,7-bis(4-hydroxyphenyl)-1,4,6-heptatrien-3-one (BHPHTO) and bisdemethoxycurcumin (BDMC), were isolated from the rhizome of *A. galanga* exhibited activity in human melanoma A2058 and demonstrated that it significantly inhibited melanoma cell proliferation in the cell viability assay (MTT assay) at a concentration of 50 µM. The cell viability showed less than 25% after 24 h of

treatment. This study was also carried out on the B16-F10 cell line and showed minor inhibition of tyrosinase activity and melanin content (Lo et al., 2013). The mechanism of *Alpinia galanga* showed by Figure 35.

### 3.35. *Annona Muricata L.*

*Annona muricata* L. is a tree about 5–6 m tall, growing in tropical South America and North America, especially in the Amazon. The sweet oval fruit is prickly and has white flesh inside a dark green or yellow-green peel. The peels, leaves, roots, and seeds of soursop have been used in traditional medicine, and plant parts have different effects and uses (Asare et al. 2015). It contains bioactive compounds such as alkaloids, flavonoids, tannins, and phenolic compounds (Gajalakshmi et al., 2012), which have excellent antioxidant effects due to the abundance of polyphenols and are effective against headaches, hypertension, coughs, and asthma.

In recent applications, it has been used as an antispasmodic agent for the treatment of cardiac conditions and as a sedative and sedative agent (Lans, 2006; Baskar et al. 2007). In addition, the active components of the leaves and seeds have a cytotoxic effect on cancer cells (Baskar et al. 2007). The study by Joo et al. (2017) found that a decrease in melanin content after treatment with *A. muricata* L. extract (concentration 60 µg/mL) showed a skin-whitening effect, and this change was the effect of a decrease in tyrosinase activity in melanoma cells. B16F10 mice.

Moreover, tyrosinase mRNA and protein expression levels were regulated by *A. muricata* L. extract. The MITF mRNA expression level decreased in the presence of *A. muricata* L. extract (Joo et al., 2017). The mechanism of *Annona muricata* L. showed by Figure 36.

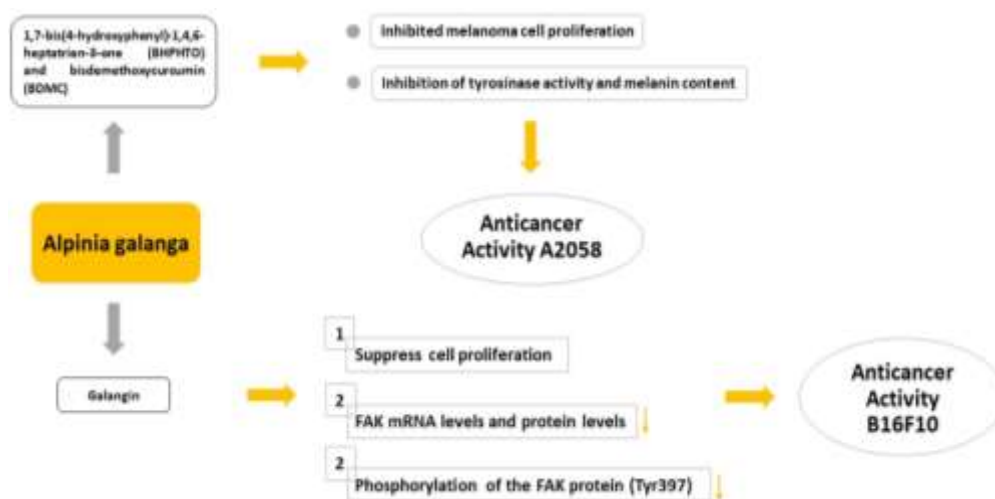


Figure 35. The mechanism of *Alpinia galanga*.

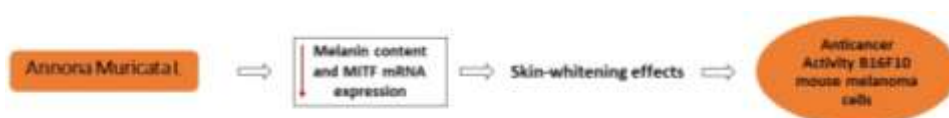
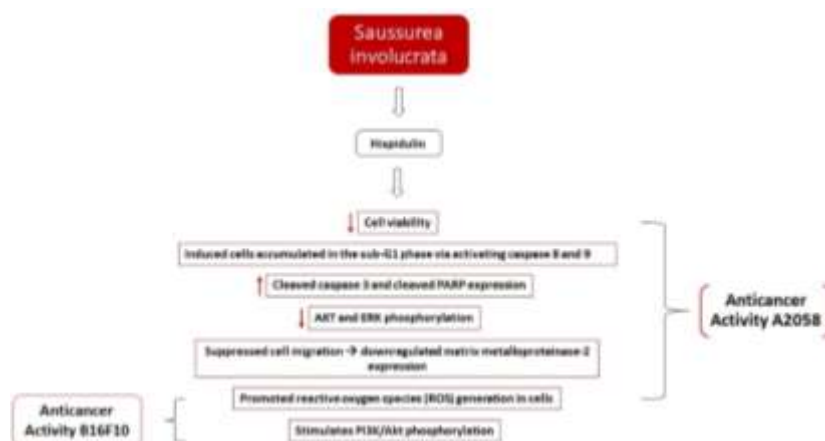


Figure 36. The mechanism of *Annona muricata* L.

### 3.36. *Saussurea involucreta*

*Saussurea involucreta* Matsum. & Koidz is an endangered species of the Asteraceae family, growing in the high mountains of central Asia. It has been, and is, widely used in traditional Uyghur, Mongolian, and Kazakhstan medicine as well as in Traditional Chinese Medicine as Tianshan Snow Lotus (Chinese). Empirically, *S. involucreta* promotes blood circulation, alleviating all symptoms associated with poor circulation (Chik et al., 2015). Several pharmacological activities of *S. involucreta* have been reported, including anti-inflammatory, antioxidant, rheumatoid arthritis, cough and cold, abdominal pain, dysmenorrhea, and anticancer effects (prostate cancer, gastric cancer, breast cancer). Recently, *S. involucreta* has been deeply researched regarding its activity in COVID-19 treatment (Wang, et al., 2018; Gong, et al., 2020; Zhang et al., 2022). Hispidulin (4',5,7-trihydroxy-6-methoxyflavone) is a flavone derivative isolated mainly from *S. involucreta*, a medicinal plant traditionally used in oriental medicine (Xu et al., 2009). Hispidulin selectively decreased the cell viability of A2058 cells in a dose- and time-dependent

manner. Hispidulin induces cells accumulated in the sub-G1 phase via activating caspase 8 and 9, increased cleaved caspase 3, and cleaved PARP expression. Hispidulin decreased AKT and ERK phosphorylation, which facilitated cell growth and survival. Moreover, hispidulin promoted reactive oxygen species generation in cells and suppressed cell migration through downregulated matrix metalloproteinase-2 expression. Hispidulin significantly inhibited tumor growth in a xenograft model (Chang et al., 2021). *S. Involucretae* Herba attenuates ROS formation after UV-induced damage in B16F10 cells in a dose-dependent manner. Moreover, the transcriptional and translational anti-oxidative encoding genes were upregulated under SIH. Further studies showed that SIH activated the transcriptional activity of the antioxidant response element (ARE). Moreover, we found that SIH dramatically stimulates PI3K/Akt phosphorylation in cultured B16F10 cells. This result was further verified by its specific inhibitors, LY294002 and Tocris (Gong et al., 2020). The mechanism of *Saussurea involucreta* showed by Figure 37.



**Figure 37.** The mechanism of *Saussurea involucreta*.

### 3.37. *Curcuma wenyujin*

*Curcuma wenyujin* is a perennial herbaceous plant distributed in tropical and subtropical regions and primarily cultivated in Zhejiang Province, China (Fang et al., 2006). *C. wenyujin* contains terpenes, especially sesquiterpenes, which are abundant in the roots and rhizomes of *C. wenyujin*. In vivo and in vitro pharmacological experiments of *C. wenyujin* have indicated that extracts or active compounds provided antibacterial, antiviral, anti-inflammatory, antitumor, antioxidant, antifungal, and hepatoprotective activities (Liu et al., 2019; Li et al., 2019). Curcumol is one of the phytochemicals isolated from *C. wenyujin*. It decreases mouse melanoma B16 cell proliferation and migration. In addition, the xenograft tumor assay showed that curcumol reduced melanoma volume and lung metastasis. Curcumol upregulated the expression of E-cadherin and downregulated the expression of N-cadherin, MMP2, and MMP9 in mouse melanoma B16 cells. Western blot analysis revealed that curcumol reduced the translocation of p65 to the nucleus and decreased p-ERK. Furthermore, curcumol attenuated c-MET, P13K, p-AKT protein expression, and upregulated miR-152-3p gene expression. The dual-luciferase reporter assay indicated that c-MET was a target gene of miR-152-3p. Reduced expression of miR-152-3p partially attenuated the effect of curcumol on mouse

melanoma B16 cell proliferation and migration. The decrease in c-MET, P13K, and p-AKT protein expression following curcumol treatment in mouse melanoma B16 cells was notably attenuated by the miR-152-3p inhibitor (Ning et al., 2020). The mechanism of *Curcuma wenyujin* showed by **Figure 38**.

### 3.38. *Sorghum bicolor* (*S. bicolor*)

*Sorghum bicolor* belongs to the family Poaceae, is considered an important crop in tropical regions, including Africa, Central America, and arid regions, and is the fourth most important cereal crop in the world after wheat, rice, and maize (Dillon et al., 2007). *S. bicolor* contains phenolic compounds, tannins, and anthocyanins (Svensson, et al., 2010). Ethanol extract of *S. bicolor* effectively inhibited melanin production in IBMX-induced B16/F10 melanoma cells. Ethanol extract of *S. bicolor* downregulated melanogenesis by decreasing the expression of microphthalmia-associated transcription factor (MITF), tyrosinase, and tyrosinase-related protein (TRP)-1 (Han et al., 2020). Sorghum ethanolic extract (SEE) inhibited  $\alpha$ -MSH-induced Pax3 expression. The collective results indicate that SEE attenuates  $\alpha$ -MSH-induced TYR expression by suppressing Pax3-mediated MITF gene promoter activity (Lee et al., 2018). The experiment is still limited, especially in vivo assay related to its activity against melanoma skin cancer. The mechanism of *Zingiber officinale Roscoe* showed by **Figure 39**.



Figure 38. The mechanism of *Curcuma wenyujin*.

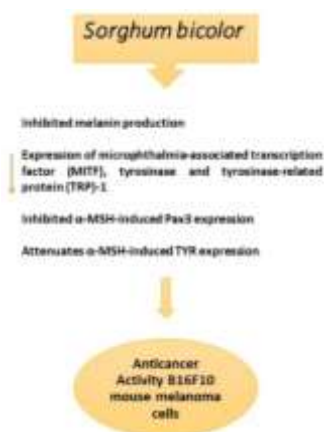


Figure 39. The mechanism of *Zingiber officinale* Roscoe.

3.39. *Murraya Tetramera*

The genus *Murraya* (family Rutaceae) is a common plant source of polymethoxylated and polyhydroxylated flavonoids (Liang et al., 2020). *M. tetramera* Huang is a small tree widely distributed in Guangxi and Yunnan provinces of China. Folk medicine has been applied to treat coughs, bronchitis, rheumatism, asthma, and traumatic injury (Lv et al., 2015). 5,3',5'-trihydroxy-6,7,4'-trimethoxyflavone (Kinoshita et al., 1996), 5-hydroxy-6,7,3',4',5'-pentamethoxyflavone (Rwangabo et al., 1988), and 2'-hydroxy-3,4,5,4',5',6' hexamethoxychalcone (Gupta et al., 1979) was successfully isolated from *M. tetramera* which proved has anti melanoma skin cancer. *M. tetramera* exhibited potent cytotoxic activities against B16 cell lines (IC50 = 3.87, 7.00, and 8.66 µg/mL, respectively) (You et al., 2021). No in vivo study found *M. tetramera* as anti-melanoma skin cancer yet. The mechanism of *Sorghum bicolor* Roscoe showed by Figure 40.

(Rwangabo et al., 1988), and 2'-hydroxy-3,4,5,4',5',6' hexamethoxychalcone (Gupta et al., 1979) was successfully isolated from *M. tetramera* which proved has anti melanoma skin cancer. *M. tetramera* exhibited potent cytotoxic activities against B16 cell lines (IC50 = 3.87, 7.00, and 8.66 µg/mL, respectively) (You et al., 2021). No in vivo study found *M. tetramera* as anti-melanoma skin cancer yet. The mechanism of *Sorghum bicolor* Roscoe showed by Figure 40.

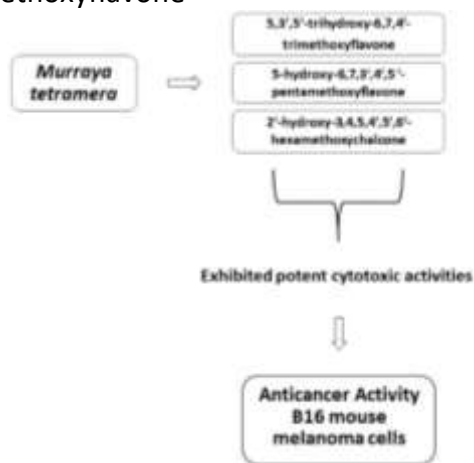


Figure 40. The mechanism of *Sorghum bicolor*.



#### 4. FUTURE PROSPECTIVES

Plants are an auspicious source of anticancer agents. They can work by inhibiting proliferation, inducing apoptosis, inhibiting migration, and inhibiting invasion in human melanoma. Many studies have reported that various plants' chemicals inhibit tumor growth in several signaling pathways. The various plants are reviewed and highlighted for their anticancer activity

(Table 2). However, studying these plants should not limit the study of many anticancer plants, some of which are still unexplored. Studies are needed to highlight the mechanism of anticancer action of many already explored and new plants. Several compounds in plants can be promising candidates for targeting melanoma skin cancer based on their in-vitro inhibition activity against melanoma skin cancer cells (Figure 41).

**Table 2.** Several of the essential anticancer medicinal plants, their active components, and in vitro activity.

Plant name	Common name	Extract used	Active component used	Cell Lines	Dose concentration	References
<i>Ailanthus altissima</i>	Tree of heaven	-	ailanthone	A-375, B16	0.25-16 µM	(Liu et al., 2020; Xiao-yu et al., 2019)
<i>Berberis aristata</i>	Tree turmeric	-	Berberine (isoquinoline alkaloid)	A-375	0, 1, 1.5 and 2 µM 0, 5, 10 and 20 µM	(Liu et al., 2018; Gupta et al., 2020)
<i>Piper betle</i> Linn	Betel	-	Bornyl cis-4-hydroxycinnamate	A-375 and A2058	1–6 µM 24 µM	(Yang et al., 2018; Wu et al., 2020)
<i>Ananas comosus</i> (L.) Merr	Pineapple	-	Bromelain	A-375, MB-F10	50–900 mg/mL 1, 12,5, 25 mg/kg	(Bhui et al., 2012; Baez et al., 2007)
<i>Passiflora caerulea</i> L.	Blue passionflower	-	Chrysin (5,7-dihydroxyflavone) (flavonoid)	A375.S2, A375, B16-F1	0, 5, 10, and 15 µM 30 µM	(Chen et al., 2018; Zeng et al., 2017; Pichichero et al., 2011)
<i>Matricaria chamomilla</i> L.	Chamomile flowers	Methanol extract	apigenin (flavanoid)	A-375, SK-MEL-2, WM1361A, C8161, A375P and A375SM	10, 30, 60 µg/mL 0,8-100 µg/ml 40-160 µM 0, 25, 50, 75 and 100 µM	(Danciu et al., 2018; Sak et al., 2017; Fraihat et al., 2018; Zhao et al., 2018; Woo et al., 2020)
<i>Glycyrrhiza spp</i>	Licorice	-	Licochalcone D Licochalcones A and E retrochalcone Licochalcone B (Lico B) Licochalcone H (LCH)	A-375 and SK-MEL-2	0, 15, 30, 45, 60, 75 and 90 µmol/l 5-20 µM 5, 10, 20, and 30 µM	(Yoo et al., 2007; Si et al., 2018; Kang et al., 2017; Park et al., 2022)
<i>Apium graveolens</i> Linn	Celery	-	Luteolin (3',4',5,7-tetrahydroxyflavone) (flavonoid)	A-375	10, 15 dan 20 µmol L <sup>-1</sup> 10 µg/mL	(Yao et al., 2019; George et al., 2013; Danciu et al., 2018)

**Table 2 (Continue).** Several of the essential anticancer medicinal plants, their active components, and in vitro activity.

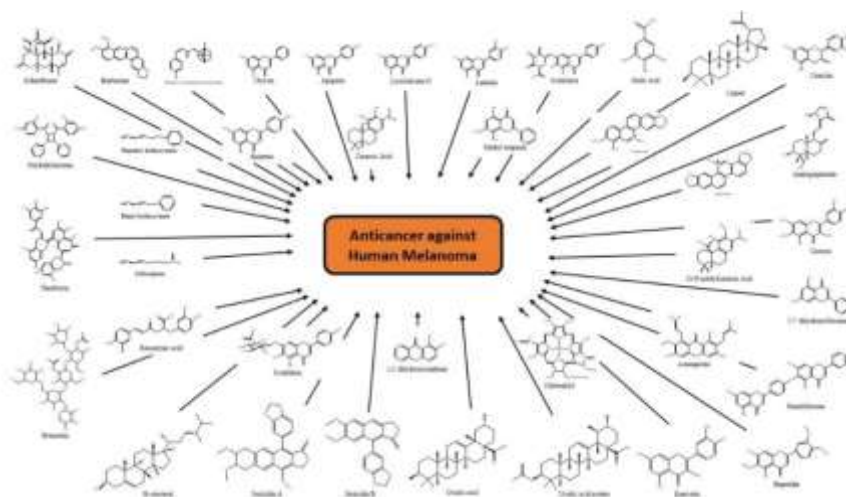
Plant name	Common name	Extract used	Active component used	Cell Lines	Dose concentration	References
<i>Oxytropis falcata</i> <i>Bunge</i>	Edaxia	Ethanol extract	Oxyfadichalcone C (chalcone)	A-375	5, 10 and 20 $\mu$ M	(Pen, et al., 2018)
<i>Erigeron breviscapus (vant.) Hand.Maz z.</i>		-	Scutellarin (flavone)	A-375 and RPMI79 51	40-160 $\mu$ M	(Liu et al., 2019; Mu et al., 2021)
<i>Camellia sinensis</i>	Tea	-	Theaflavin Epigallocatechin-3-gallate	A-375	0, 50, 100, 150, 200, 250, 300, and 400 mg/ml	(Zhang et al., 2020; Yang et al., 2017; Chen et al., 2018)
<i>Arctostaphylos caucasica</i>	Bearberry	-	3,4,5-trihydroxybenzoic acid (Gallic acid)	A-375	0, 25, 50, 100, and 200mmol/l	(Lo et al., 2011; Lo et al., 2010)
<i>Capparis decidua</i>	Karira	Hexane and chloroform extract	Lupeol, $\beta$ -sitosterol triacontenate	A-375	200, 100, 50, 25, 12.5, 6.25 $\mu$ g/mL	(AlQathama, et al., 2022; Bociort, et al., 2021)
<i>Haplophyllum tuberculatum</i>	Sazab, zeita, kheisa and mesaika	Methanol and chloroform extract	Justicidin A and B.	A-375	200, 100, 50, 25, 12.5, 6.25 $\mu$ g/mL	(Bociort et al., 2021; Al-Qathama et al., 2017)
<i>Carissa edulis</i>	Simple spined num-num	Hexane and chloroform extract	Ursolic acid, ursolic acid acetate, and quercetin	A-375	15 $\mu$ g/mL 10, 20, 30, 50, 75 $\mu$ M	(AlQathama et al., 2022; Sass et al., 2012; Srivastava et al., 2019)
<i>Artemisia L.</i>	Mugwort	Ethanol extract	Eupatilin (5,7-dihydroxy-3',4', 6-trimethoxyflavone) (flavonoid) Sesquiterpene	A-375, B16F10	0, 25, 50, 100, 200, 400, and 800 $\mu$ M	(Shawi et al., 2011; Rabe et al., 2015; Russo et al., 2020; Woo et al., 2019).
<i>Pinus maritima</i>	Maritime pine	-	Catechin	A-375	2,5, 0,5, and 0,1 mg/mL	(Thaichinda et al., 2020; Tong et al., 2015; Thaichinda et al., 2020; Singh and Katiyar, 2011)
<i>Andrographis paniculata</i>	King of bitters, kalmegh	-	Andrographolide	A-375, C8161, B16F-10, C57BL/6, B16 and HT-29	12.07 - 23.08 $\mu$ M	(Liu et al., 2018; Sa-Ngiamsuntorn et al., 2021; Sheeja et al., 2007; Rajagopal et al., 2003)

**Table 2 (Continue).** Several of the essential anticancer medicinal plants, their active components, and in vitro activity.

Plant name	Common name	Extract used	Active component used	Cell Lines	Dose concentration	References
<i>Vitex rotundifolia</i> L.	Beach vitex	-	Casticin	A-375	3.84 $\mu$ M	(Shiue et al., 2016)
<i>Galenia africana</i>	Kraalbos, geelbos	Ethanollic extract	5,7-dihydroxyflavone, (2S)-5,7,2'-trihydroxyflavone, (E)-3,2',4'-trihydroxychalcone, and (E)-2',4'-dihydroxychalcone, and the new (E)-3,2',4'-trihydroxy-3'-methoxychalcone	A-375, B16F10	500 - 1000 $\mu$ g/mL	(Heredia et al., 2022; Ndlovu et al., 2021; Mativandlela et al., 2009; Zheng et al., 2018)
<i>Selaginella P. Beauv</i>	Spike-moss, peacock fern	Aqueous and Ethanollic extract	hinokiflavone	A-375, B16	8 $\mu$ M - 23 $\mu$ M	(Yang et al., 2018b; Bailly et al., 2021; Francois et al., 2021)
<i>Brassica oleracea</i> L.	Kohlrabi; stem turnip	-	Phenethyl Isothiocyanate, Benzyl Isothiocyanate, dan Sulforaphane	A-375	5–15 $\mu$ M	(Yan et al., 2009)
<i>Rosmarinus officinalis</i> L.	Rosemary	Ethanollic extract	Rosmarinic acid, Apigenin, Scutellarin, and Carnosic Acid	A-375, M14	20-40 $\mu$ g/mL	(Russo et al., 2009)
<i>Sanguinaria canadensis</i>	Bloodroot	Ethanollic extract	Sanguinarine and chelerythrine	A-375, B16, B16F0, SK-MEL-2, K1735-M, G361, SKMEL3	0.11–0.54 $\mu$ g/mL	(Tuzimski et al., 2021; Serafim et al., 2008; Hammerova et al., 2011)
<i>Salvia pomifera</i> L.	Apple sage	Methanollic extracts	12-O-methylcarnosic acid	A-375	70.29 $\mu$ g/mL	(Koutsoulas et al., 2019)
<i>Salvia fruticosa</i> Mill.	Greek sage, greek oregano	Methanollic fraction	Carnosic acid	A-375, Mel JuSo	7.56-57.95	(Koutsoulas et al., 2019)
<i>Garcinia mangostana</i> L.	Mangosteen, Xanton	-	Xanton/ $\alpha$ -mangostin and 1,2-dihydroxyxanthone	A-375 and SK-MEL-28, A375-C5	15 $\mu$ M	(Markowicz et al., 2019; Wang et al., 2017)

**Table 2 (Continue).** Several of the essential anticancer medicinal plants, their active components, and in vitro activity.

Plant name	Common name	Extract used	Active component used	Cell Lines	Dose concentration	References
<i>Citrus grandis</i> (Linn.) <i>Osbeck</i>	Pomelo	-	chlorophyll and carotenoid	A-375	3.3 - 4.2 µg/mL	(Liu, et al., 2021; Liu, et al., 2021; Nasr bouzaiene, et al., 2015)
<i>Lycopodium clavatum</i>	Running clubmoss	Ethanol extract	Apigenin	A-375, B16F10, and SK-MEL-24	20 to 250 µg/mL	(Das, et al., 2012; Ghiţu, et al., 2021)
<i>Trametes robiniophila</i> Murr	Sandy beige mushroom	-	Proteoglikan	A-375	(4, 8, and 16mg/mL	(Su, et al., 2020)
<i>Scutellaria baicalensis</i>	Baikal skullcap or Chinese skullcap	-	methylwogonin	A-375, B16F10	0, 50, 150, to 300 µM	(Chen, et al., 2017; Choi, et al., 2017)
<i>Zingiber officinale</i>	Ginger	Ethanol extract	Zerumbone (ZER)	A2058, B16F10	0, 0,2, dan 0,4 mg/mL	(Guon et al., 2016; Oh et al., 2018)
<i>Roscoe Curcuma longa</i>	Turmeric	-	Curcumin/curcuminoid	A-375, B16	20 µM 12,5, 25, dan 50 µM 100 mg/mL	(Zhang et al., 2015; Kim et al., 2008)
<i>Alpinia galangal</i>	galangal	-	1,7-bis(4-hidroksifenil)-1,4,6-heptatrien-3-one (BHPHTO) dan bisdemethoxycurcumin (BDMC)	A2058, B16F10	50 µM	(Lo et al., 2013)
<i>Annona muricata</i> L.	soursop	-	-	B16F10	60 µg/mL	(Joo et al., 2017)
<i>Saussurea involucrata</i>	snow lotus, qust/kustha	-	Hispidulin (4',5,7-trihydroxy-6-methoxyflavone)	A2058, B16F10	1–50 µM	(Xu et al., 2009; Chang et al., 2021; Gong et al., 2020)
<i>Curcuma wenyujin</i>	Wild turmeric	Ethanol extract	Curcumol	B16	0, 25, 50, 100 and 200 µM	(Ning et al., 2020).
<i>Sorghum bicolor</i> (S. bicolor)	Sorghum, great millet, milo, durra	Ethanol extract	-	B16F10	89.25 µg/mL	(Han et al., 2020; Lee et al., 2018)
<i>Murraya tetramera</i>	Murraya	-	5,3',5'-trihydroxy-6,7,4'-trimethoxyflavone, 5-hydroxy-6,7,3',4',5-pentamethoxyflavone, and 2'-hydroxy-3,4,5,4',5',6'-hexamethoxychalcone	B16	3.87, 7.00 and 8.66 µg/mL	(You et al., 2021).



**Figure 41.** Bioactive compounds which act as anti-melanoma skin cancer.

## 5. CONCLUSION

This review article determined natural products from medicinal plants which have the potential as an anticancer in melanoma skin cancer in vitro and in vivo. 40 plants have been selected based on the selection criteria for anticancer compounds.

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## 7. AUTHORS' NOTE

The author(s) declare(s) that there is no conflict of interest regarding the publication of this article. The authors confirmed that the data and the paper are free of plagiarism.

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